U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Moussa C. Mansour, MD 3/18/14

Department of Health and Human Services

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

March 18, 2014

WARNING LETTER

VIA UNITED PARCEL SERVICE

Moussa C. Mansour, MD
Massachusetts General Hospital, GBR 109
55 Fruit Street
Boston, MA 02114

Dear Dr. Mansour:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection at your clinical site from August 12, 2013, to October 15, 2013, by investigators from the FDA's New England District Office. This inspection was conducted to determine whether your activities and procedures as a clinical investigator complied with applicable federal regulations. The clinical studies addressed in this letter include:

- "WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation **(PROTECT-AF)**" for the Watchman Left Atrial Appendage System, Investigational Device Exemption (IDE) **(b)(4)**
- "WATCHMAN Left Atrial Appendage System Continued Access AF Registry – **(CAP Registry)**" for the Watchman Left Atrial Appendage System, IDE **(b)(4)**
- "Prospective Randomized EVAluation of the WATCHMAN LAA Closure Device In Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy **(PREVAIL)**" for the Watchman Left Atrial Appendage System, IDE **(b)(4)**

- "Continued Access Protocol for the Evaluation of Catheter Cryoablation in the Treatment of Paroxysmal Atrial Fibrillation **(CAP-AF)**" for the 7F Arctic Circler Curvilinear Cardiac Cryoablation Catheter, IDE **(b)(4)**

The Watchman LAA Closure Device and the Cryocath Technologies 7F Arctic Circler Curvilinear Cardiac Cryoablation Catheter are devices as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 USC § 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. This letter also requests prompt corrective action to address the violations cited and discusses your written response dated November 4, 2013, 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, which concerns requirements prescribed under section 520(g) (21 USC 360j(g)) of the Act. At the close of the inspection, the FDA investigator presented the 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 an investigation was conducted in accordance with the investigational plan. [21 CFR 812.100 and 812.110(b)]

As a clinical investigator (CI), you are responsible for ensuring that an investigation is conducted according to the investigational plan. You failed to adhere to these regulations by not ensuring that qualified study staff were delegated to perform assessments and that the staff were appropriately trained. In addition, you failed to submit several serious adverse events (SAEs) to the sponsor within the timeframe specified in the study protocol. Examples of this include, but are not limited to, the following:

a. Protocol section 6.6, "Follow-up Requirements," for the CAP Registry study, states that, "Neurological assessment by a neurologist" must be performed at **(b)(4), (b)(4),** and **(b)(4)** follow-up time points. However, at these follow-up time points, neurological assessments were performed by either **(b)(4),** or by study coordinator **(b)(4)** as shown below.

Subject No.	Visit Date	Signature on Worksheet
(b)(4), (b)(6)		

Neither **(b)(4)** nor **(b)(4)** are listed in your delegation of authority logs or other study records identifying them as neurologists who are qualified to perform these neurological assessments. Thus, **(b)(4)** and study coordinator **(b)(4)** were not properly delegated to perform these neurological assessments. Study related procedures must be performed by designated individuals with proper training and expertise. This helps ensure that study subjects will receive prompt and appropriate treatment should any medical complications or study related adverse events occur.

In addition to your written response November 4, 2013, to the above violations, FDA received two letters from your IRB dated December 16, 2011, and May 31, 2012, that identify problems with the neurology assessments in the study and that show that you initiated a corrective action plan (CAP). However, your response is inadequate because your CAP does not include an explicit process for checking that staff members have appropriate credentials. Also, your CAP does not prohibit a neurologist from further delegating tasks to others who work independently and are not qualified or appropriately trained.

Please provide a preventative action plan detailing how you will ensure that qualified study staff members are appropriately delegated in future studies. Also provide new and/or revised standard operating procedures (SOPs)/checklists to address the above violations and an updated list of study staff trained, dates trained, and dates of implementation.

b. For the PREVAIL study, your site's "Delegation and Signature Log" notes that **(b)(4)** and **(b)(4)** are delegated to perform trans-esophageal echocardiography (TEE). However, study records for several subjects show that TEEs for these subjects were performed by non-study staff and there is no documentation to show that they received appropriate training prior to performing TEEs. Examples of TEE performed by non-study staff include:

Subject No. Visit Dates (Initials of Signing Staff)
(b)(4), (b)(6)

Your failure to ensure that TEEs were performed only by designated and adequately trained study staff is a serious violation of your responsibilities under the investigational plan. TEEs are a critical component of the study and your actions could compromise the accuracy and reliability of the data from these tests.

Your written response, dated November 4, 2013, to the above violations is inadequate. It states, "When I discovered a few months ago that not all TEEs were performed by **(b)(4),** I discussed it with **(b)(4). (b)(4)** assured me that the individuals who performed the TEEs were trained by **(b)(4)** on the imaging protocol." However, there is no documentation to verify that this training took place. In addition, you have failed to provide an updated delegation and signature log to show that these non-study staff members are now listed to perform TEEs.

Please provide a preventative action plan detailing how you will ensure that only designated and adequately trained study staff members perform study related procedures in future clinical studies. In addition, please provide new and/or revised

SOPs/checklists to address the above violations and an updated list of study staff members trained, dates trained, and dates of implementation. Also, please submit an updated delegation and signature log.

c. For the PROTECT-AF, PREVAIL, and CAP-AF studies, you failed to report SAEs to the sponsor in a timely manner as stipulated in accordance with the protocols. There was no documentation maintained at your site to show that SAEs were reported to the sponsor for these studies. You were reminded by the study monitor in a letter dated May 14, 2010, that there were many possible SAEs noted upon review of the records and that SAE CRFs were found in the study binder that had not been properly transmitted to the sponsor. Examples of SAEs that were not reported appropriately include:

i. Section 6.7 of the PROTECT-AF protocol stipulates that the sponsor must be notified of SAEs within **(b)(4)** of the investigator learning of the event. The study monitor had reminded you of possible SAEs in a follow-up letter dated May 14, 2010. **(b)(4)** recent examples from the PROTECT-AF study are listed below from a list of SAEs that the sponsor had provided during the inspection:

Subject No.	Date Site Notified	Date Sponsor Notified
(b)(4), (b)(6)		

ii. Section J(ii) of the PREVAIL protocol states that SAEs, "are to be reported to **(b)(4), (b)(4)** of learning of the event." However, you failed to document that SAEs were reported within this timeframe for subjects **(b)(4), (b)(6)**. We acknowledge that you have a written note on file that states that the SAE for Subject **(b)(4), (b)(6)** was sent, but the date that the SAE was sent was not indicated.

iii. Section 11.2 of the CAP-AF study protocol states that SAEs must be reported to the sponsor within **(b)(4)** of becoming aware of the event. However, your staff reported untimely SAEs from **(b)(4)** to **(b)(4)** later for certain subjects Examples are listed below:

Subject No.	Date Aware	Notification Date
(b)(4), (b)(6)		

By not providing timely reporting of SAEs, you may have compromised the integrity of the data in the study.

As part of your CAP, you provided training on the reporting of adverse events to your research staff and described a plan to monitor adverse events **(b)(4)** with **(b)(4)** audits. However, you failed to explain how you plan to ensure that SAEs are reported to the sponsor within the **(b)(4)** or **(b)(4)** limits for the protocols in the studies above.

Your written response dated November 4, 2013, explains that all research staff are instructed to report adverse events to you and/or to one of the study coordinators as soon as possible. This response to the violations noted is inadequate because you do not explain how you will ensure that the adverse events are reported to the sponsor according to the investigational plan.

Please explain the cause of the lack of timely reporting of SAEs and ensure that all SAEs have been appropriately documented. In addition, please provide a preventative action plan detailing how you will ensure the timely reporting of SAEs according to time frames specified in future studies. Also, please provide any new and/or revised SOPs/checklists to address the above violations.

2. Failure to maintain accurate, complete and current records regarding correspondence with the IRB [21 CFR 812.140 (a)(1)]

A clinical investigator must maintain an accurate, complete, and current record of all correspondence with the IRB. Listed below are examples where you have failed to meet this requirement. For example:

a. For the PROTECT-AF and CAP Registry studies,the study records indicate that subjects **(b)(4), (b)(6)** and **(b)(4), (b)(6)** had successfully completed the study. However, your staff reported to the IRB on September 6, 2005 and August 16, 2006 that the subjects **(b)(4), (b)(6)**.

Your failure to accurately report to the IRB the **(b)(4)** of study subjects under your care is a serious violation of your responsibility as a clinical investigator. Proper reporting of study related events, especially subject **(b)(4)**, to the IRB is an important part in ensuring the safety and welfare of all study subjects as these reports provide vital information on the study's progress to the reviewing IRB. This information helps the IRB evaluate and decide whether changes need to be made to the study to continue to ensure subject safety.

Your CAP is inadequate because it does not specifically address the issue of how you will verify information on items of correspondence to the IRB before signing them. Also, you explained in your written response dated November 4, 2013, that your study coordinator had **(b)(4), (b)(6).** Your written response is inadequate because it does not propose corrective or preventative actions to address how the deficiencies will be avoided in the future.

Please provide a preventative action plan detailing how you will review and verify study data to ensure that information reported to the IRB is accurate, complete, and current. Also, please provide new and/or revised SOPs/checklists to address the above violations.

b. For the CAP-AF study, you inaccurately reported adverse events to the IRB in Continuing Review reports. According to reports dated **(b)(4)** and **(b)(4)**, you stated that **(b)(4)."** However, the study records indicate that adverse events had been reported to you throughout the course of the study. Despite this, no adverse events were reported to the IRB until the **(b)(4)** Continuing Review report **(b)(4).**

Not accurately reporting adverse events can compromise the integrity of the data in this study. Your CAP states that you will be monitoring adverse events and that you provided training to your research staff on adverse event reporting. This is incomplete because it does not specify how monitoring of AEs will occur.

Additionally, in your written response dated November 4, 2013, you stated, "I delegated tasks to the research coordinator, **(b)(4)**. whom I believed had the experience to perform these tasks." Your written response is inadequate because it does not propose corrective or preventative actions to address how the deficiencies will be avoided in the future.

Please provide a preventative action plan detailing further measures that you will take to ensure that you and your staff will be adequately trained, so AEs and SAEs are appropriately reported in future studies.

We also note that, for the PREVAIL study, you signed neurological assessment worksheets that appear to have been completed by the study coordinator **(b)(4)** but **(b)(4)** was not employed at the hospital at the time of the subject visits. Handwritten notes on monitor reports from later dates, which appear to be from this study coordinator, state that no documentation for the neurologist exam could be found; however, the signed worksheets did exist and were found in a separate folder outside of the subject records. Examples of subject files that are questionable include the **(b)(4)** neurology assessments for Subjects **(b)(4), (b)(6)** and **(b)(4), (b)(6)**.

We request that you provide a preventative action plan detailing additional measures beyond the CAP that you will take to ensure proper oversight and accurate documentation of current and future research studies under your purview. In addition, please provide new and/or revised SOPs/checklists to address the above violations.

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

Within 15 working days of receiving this letter, please provide documentation of additionalactions 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. In addition, 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.

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/ (http://www.fda.gov/oc/ohrt/irbs/)**. Any submitted corrective action plan must include projected completion dates for each action to be accomplished and a plan for monitoring the effectiveness of your corrective actions.

Your response should reference “CTS P130013/E001” and be sent to:

Attention: Albert Rodriguez
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3456
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to FDA’s New England District Office, One Montvale Ave., 4th Floor, Stoneham, MA 02180. 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 (http://www.fda.gov/Training/CDRHLearn/ucm162015.htm)**.

If you have any questions, please contact William Riemenschneider at 301-796-9682 or by e-mail at **Bill.Riemenschneider@fda.hhs.gov (mailto:Bill.Riemenschneider@fda.hhs.gov)**.

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

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