WARNING LETTER

Nobles Medical Technology II, Inc.

MARCS-CMS 673465 — JANUARY 26, 2024

Product:

Medical Devices

Recipient:

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WARNING LETTER

January 26, 2024

Dear Dr. Nobles:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at Nobles Medical Technology II, Inc. from October 16, 2023, to October 20, 2023, by investigators from the FDA's Office of Bioresearch Monitoring Operations (OBIMO). This inspection was conducted to determine whether activities and procedures as sponsor in the significant risk clinical study "STITCH - Prospective Multi-Center Comparative Parallel Concurrent Study of the NobleStitch EL versus FDA approved Amplatzer Occluder device for closure of Patent Foramen Ovale to prevent recurrent ischemic stroke," for NobleStitch EL, Investigational Device Exemption (IDE), G180296, complied with applicable federal regulations. The NobleStitch EL 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), 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 also requests prompt corrective action to address the violations cited.

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

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course of scientific investigations.

Our review of the inspection report prepared by the OBIMO revealed serious violations of Title 21, Code of Federal Regulations (CFR) Part 812 - Investigational Device Exemptions, 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 your review and discussed the observations listed on the form with you. To date, your firm has not submitted a written response. The deviations noted on the Form FDA-483 and our subsequent review of the inspection report, are discussed below:

1. Failure to ensure proper monitoring and Institutional Review Board (IRB) review and approval [21 CFR 812.40].

As a sponsor, you are responsible for providing investigators with the information they need to conduct the investigation properly and for ensuring proper monitoring of the investigation. You are also responsible for ensuring that IRB review and approval are obtained and that the IRB and FDA are promptly informed of significant new information about an investigation. Examples of your failure include, but are not limited to, the following:

a. You failed to provide investigators with necessary information to properly conduct the study, including but not limited to, signed protocols, investigational brochures, and labeling.

b. You failed to ensure proper monitoring of the study. Examples include, but are not limited to:

- Lack of a written monitoring plan and procedures describing how you will monitor the investigation, including how to handle protocol deviations and investigator noncompliance.
- Site monitoring reports do not include the documents reviewed, associated findings, and communications with site personnel, including whether your site monitoring included a comparison of source documents with Case Report Forms (CRFs), an essential component of a monitoring plan to ensure data integrity.
- Additionally, you failed to secure investigator signatures on CRFs in a timely manner per the Investigator Agreement Section 10.1 (Trial Documentation). For example, Investigator **(b)(6)** signed four CRFs eight to twelve months after their monitoring visits, and Investigators **(b)(6)** and **(b)(6)** did not sign nine and two CRFs, respectively, for monitoring visits to their sites.

c. You failed to provide documentation of IRB approvals and continuing review for site **(b)(4)** and IRB approval for sites **(b)(4)** and **(b)(4)** for the protocol (versions 5 and 6) and the Amplatzer and NobleStitch CRFs.

Proper monitoring helps ensure that the safety, rights, and well-being of the subjects are protected, and that the data are complete and accurate. Monitoring should be an on-going program performed with the frequency necessary to ensure that the investigation is conducted according to the investigational plan, FDA regulations, and any conditions of approval required by the FDA or the reviewing IRB. Inadequate monitoring can lead to reporting of inaccurate data, missing data, enrollment of subjects that do not meet eligibility criteria, and poor adverse event reporting, among other concerns. In addition, without adequate monitoring there is no assurance that your study conduct is compliant and that any instances of noncompliance are resolved properly.

Furthermore, your failure to ensure that IRB review and approval was obtained at least annually, delays, or prevents the IRB from considering any changes in the research or research-related events and determining whether the human subject protection measures are adequate or need to be changed. Lastly, inadequate oversight of investigator activities can also significantly impact conduct of the study and therefore, the reliability of data generated in the study as well as the safety of study participants.

2. Failure to select qualified investigators and monitors by training and experience for conducting of a study [812.43(a) and (d)].

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As a sponsor, you are responsible for selecting qualified investigators and monitors. Examples of your failure include, but are not limited to, the following:

a. You failed to ensure that clinical investigators were qualified by training and experience to conduct the study. During the inspection, you did not provide documentation, such as a curriculum vitae, to show that the clinical investigators were qualified to conduct this study.

b. You did not provide documentation to support that you have the proper training and experience to appropriately monitor the study.

The selection of qualified investigators and monitors is essential to ensure subjects' safety and that your study is conducted properly in accordance with Good Clinical Practices.

3. Failure to obtain a signed agreement from each participating investigator that includes a statement of the investigator's commitment to conduct an investigation in accordance with the agreement, investigational plan, applicable FDA regulations, conditions of approval imposed by the reviewing IRB and conditions of approval imposed by the FDA [21 CFR 812.43(c)(4)(i)].

As a sponsor, you are responsible for obtaining from each participating investigator a signed agreement that includes a statement of the investigator's commitment to conduct the investigation in accordance with the agreement, the investigational plan, and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA.

While signed agreements were obtained of participating clinical investigators, they lack a statement of the investigator's commitment to supervise all testing of the device involving human subjects. Obtaining signed agreements is important for ensuring that investigators participating in the clinical study are accountable for the conduct of the study.

4. Failure to obtain from each participating investigator a signed agreement that includes sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement [21 CFR 812.43(c)(5)].

As a sponsor you are responsible for obtaining from each participating investigator a signed agreement that includes sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement.

You failed to obtain a signed agreement that includes sufficient accurate financial disclosure information from each participating investigator. Specifically, you did not provide financial disclosure records for any site during your inspection. Obtaining accurate financial disclosure information is important for ensuring that there is no financial bias by any of your clinical investigators that may impact clinical study data.

In addition to the above objectionable conditions found during the inspection of your U.S. sites, there were similar observations noted for your site in Italy, which is your largest enrolling site. These observations include inadequate study protocols, lack of investigator agreements, inadequate informed consent, inadequate adverse event reporting, inadequate investigational device tracking, and inadequate monitoring.

All of these failures raise significant concerns regarding whether your study will yield credible and accurate data and whether the rights, safety and well-being of subjects are adequately protected. The consequences of these failures are evidenced by the decision to suspend your study and the numerous cycles of review of your annual reports for the IDE, where discrepant and unclear information has been provided regarding fundamental aspects of your study (e.g., reviewing IRBs and sites and numbers of enrolled/implanted subjects) as well as safety and effectiveness information.

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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 study sponsor to ensure compliance with the Act and applicable regulations.

Within 15 working days of receiving this letter, please provide documentation of the corrective and preventative 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 study sponsor. Any submitted corrective action plan must include projected completion dates for each action to be accomplished as well as a plan for monitoring 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# G180296/E003” and be sent via email to: Albert.Rodriguez@fda.hhs.gov.

A copy of this letter has been sent to FDA’s OBIMO West via email ORABIMOW.Correspondence@fda.hhs.gov. Please send a copy of your response to that office.

The Division of Clinical Policy and Quality 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.

If you have any questions, you may contact Alejandra Cambonchi by phone at (301) 796-0552 or email at Alejandra.Cambonchi@fda.hhs.gov.

Sincerely yours,
/S/

Soma Kalb, PhD
Director
Division of Clinical Policy and Quality
Office of Clinical Evidence & Analysis
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Center for Devices and Radiological Health

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