U.S. Department of Health & Human Services

U.S. Food and Drug Administration
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Inspections, Compliance, Enforcement, and Criminal Investigations

Malcolm, Matthew PhD., OTR 5/22/12

Department of Health and Human Services

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

VIA UNITED PARCEL SERVICE

WARNING LETTER

May 22, 201

Matthew P. Malcolm, PhD, OTR
Associate Professor & Director
Colorado State University
NeuroRehabilitation Lab
Department of Occupational Therapy
College of Applied Human Sciences
800 Oval Drive
Fort Collins, CO 80523-1573

Dear Dr. Malcolm:

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 February 10, 2012, to February 16, 2012, by investigators from the FDA Denver District Office. This inspection was conducted to determine whether activities as the sponsor-investigator of the clinical study, "*Repetitive Transcranial Magnetic Stimulation (rTMS) as an Adjunct to Constraint-Induced Therapy: a Randomized Controlled Trial of the Magstim Rapid Stimulator*," Investigational Device Exemption (IDE) **(b)(4)**, complied with applicable federal regulations. This letter requests prompt corrective action to address the violations cited and discusses your written response dated February 28, 2012, to the noted violations.

The Magstim Rapid Stimulator 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.

The inspection was conducted under a program designed to ensure that data and information contained in requests for IDE, premarket approval applications, and premarket notification submissions are scientifically vali 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 o 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 your review and discussed with you the observations listed on the form. 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)(2) and 812.100].

As an investigator, you are responsible for ensuring that informed consent is obtained in accordance with 21 CFR Part 50. It is your responsibility to ensure that the informed consent document (ICD) contains all the information required by 21 CFR 50.25, such as a description of any reasonably foreseeable risks or discomforts to the patient. You failed to adhere to the above-stated regulation in that you obtained consent for all subjects using a version of the ICD that did not contain information related to risk and exclusion criteria as required by the FDA and approved by your institutional review board (IRB).

Specifically, letters from the FDA dated September 21, 2007, November 27, 2007, and August 21, 2008, required changes to the ICD to include information on the exclusion of subjects with large-stroke lesions and information related to the risk of permanent hearing loss. You received IRB approval of your revised ICD including these elements on July 30, 2007, prior to enrolling any subjects. However, all subjects signed a version of the ICD that did not contain the information required by FDA's letters and approved by your IRB.

Failure to provide subjects with complete information on the study-associated risks prevents them from understanding the scope of the study, limits their ability to make an informed decision as to their participation, and could jeopardize their safety and welfare.

In your February 28, 2012, response letter, pg. 2, Corrective action for Observation 1a, you stated that, despite obtaining IRB approval for these changes to the ICD, the study coordinator failed to use the updated versions when consenting subjects. You indicated that you will consent subjects enrolled in the future with the correct version of the ICD. Your response is inadequate in that you do not fully explain your procedure for ensuring tha site staff will access the correct ICD version in future situations. Please provide a description of this procedure and documentation of staff training on the procedure.

You indicated in your response letter, pg. 2, Corrective action for Observation 1b, that **(b)(4)**. Please provide us with copies of any communications to subjects and the results of your follow-up attempts.

2. Failure to maintain accurate, complete, and current records relating to all relevant observations including anticipated and unanticipated adverse events [21 CFR 812.140(a)(3)(ii)].

As an investigator, you are responsible for maintaining accurate, complete, and current records related to the condition of each subject throughout the course of the study, including anticipated or unanticipated adverse device effects, relevant previous medical history, and the results of all diagnostic tests. You are also responsible for documenting that you reviewed each event as per your IRB-approved protocol dated April 19, 2007. You failed to adhere to the above-stated regulations. Examples of this failure include, but are not limited to, the following:

Your protocol states that you, as the principal investigator, will report all adverse events to the IRB, the Data Safety Monitoring Committee (DSMC), and the FDA. However, seven Monthly Phone Follow-Up forms reported changes in subjects' health and you had no documentation that you reviewed these events to determine the extent to which they affected the subject's participation in the study, resulting data, or subject safety. Furthermore, there were no records to show that you reported these events to the IRB, DSMC, or FDA. The events are as follows:

- **(b)(6)**: the Month 1 Phone Follow-up Form dated January 25, 2008, identified that the subject reported partial loss of arm function and a decrease in wrist flexibility because of cold weather.
- **(b)(6)**: the Month 3 Phone Follow-up Form dated March 14, 2008, identified that the subject reported the return of a headache.
- **(b)(6)**: the Month 1 Phone Follow-up Form dated June 19, 2008, identified that the subject slipped

getting out of a truck and cut the left elbow, requiring a hospital visit to stop the bleeding.

- **(b)(6)**: the Month 2 Phone Follow-up Form dated October 17, 2008, identified that the subject complained of bumps and then blistering on her treated hand, affecting her activities.
- **(b)(6)**: the Month 3 Phone Follow-up Form dated January 12, 2009, identified that the subject reported a thyroid cyst, atypia, and required surgery.
- **(b)(6)**: the Month 1 Phone Follow-up Form dated June 5, 2009, identified that the subject reported a dro in blood pressure for a few days.
- **(b)(6)**: the Month 3 Phone Follow-up Form dated August 14, 2009, identified that the subject reported ar illness of rash, sweats, diarrhea, vomiting, and weakness, and was unable to do many activities with her stroke-affected arm.

Failing to review and report these adverse events raises concerns that you are not adequately overseeing the safety and welfare of your subjects following the investigational treatment. Incomplete documentation may alsc lead to errors in subject management, resulting in potential serious health consequences. Additionally, lack of complete record-keeping raises concerns about the integrity and reliability of your study data.

In your response letter, pg. 8, Corrective action for Observation 5i and ii, you stated that you will report advers events to the IRB and FDA in accordance with reporting requirements. Your response is inadequate in that you did not tell us how you rectified the adverse event deficiencies listed above, or provide us with your future process for obtaining and reviewing adverse events and with documentation of staff training. Please provide this information in writing.

3. Failure to maintain accurate, complete, and current records relating to each subject's case history and all relevant observations, including records showing the dates and reasons for each deviation from the protocol [21 CFR 812.140(a)(3) and 812.140(a)(4)].

As an investigator, you are responsible for maintaining accurate, complete, and current records of each subject's case history, including case report forms and supporting data. Furthermore, you are responsible for maintaining records that show the date and reason that you deviated from the protocol. For example, on severa occasions, you failed to accurately complete required fields in the screening records for several subjects or document protocol deviations when the investigational treatment was started early or interrupted.

A. Examples of incomplete subject screening records include, but are not limited to:

- **(b)(6)**: the **(b)(4)** dated October 24, 2007, documented that the subject had a seizure, which is an exclusion criterion. The DSMC later determined that this entry was a clerical error and that the subject never had a seizure. However, there is no documentation in the subject's case history that refutes or corrects this entry.
- **(b)(6)**: the **(b)(4)** dated October 24, 2007, did not record an answer for the question, "Have you had any major illnesses in the past?"
- **(b)(6)**: the **(b)(4)** dated October 23, 2007, did not record answers to three questions related to the subject's ability to complete the study or care for herself.
- **(b)(6)**: the **(b)(4)** dated October 24, 2007, did not record answers for the "Total Score" field and the "Eligible for continuation of screening" question.
- **(b)(6)**: the **(b)(4)** dated February 26, 2008, did not record an answer to the question, "Will you be available for the committed time for the study (about 1 year total)?"
- **(b)(6)**: the undated **(b)(4)** did not record an answer for the "Level of consciousness" question.

B. Your records show that **(b)(6)** was not treated with the investigational device as directed in the protocol. Specifically:

- **(b)(6)** began screening procedures on October 24, 2007, as documented by the subject's **(b)(4)**. However, the subject's personal physician did not sign the **(b)(4)**, clearing the subject to participate in the study, until November 1, 2007. There is no record documenting this deviation from the protocol.
- **(b)(6)** did not have rTMS performed on study days 6, 7, 8, and 9, as noted on the subject's **(b)(4)**. However, you did not formally document these protocol deviations and the notes on the **(b)(4)** do not go

into adequate detail in documenting the dates and reasons for the lapse in procedure.

Using inaccurate or incomplete screening data to enroll subjects and failing to receive approval from personal physicians prior to subjects' study participation may prevent you from making informed decisions regarding the appropriate inclusion of study subjects. These practices may also jeopardize study completion and the safe participation of subjects. Furthermore, failure to maintain accurate, complete, and current records, including the rationale for the protocol deviations, could jeopardize the integrity and reliability of study data.

In your response letter, Appendices 1, 2, 4, and 7, you provided copies of your revised **(b)(4)**, and your newly created **(b)(4)** for documenting events not otherwise captured in the study documents. We also request that you provide documentation of staff training on these procedures and the use of these forms.

4. Failure to prepare and submit progress reports to FDA at regular intervals and at least yearly [21 CFR 812.150(b)(5)].

As a sponsor, you are responsible for preparing and submitting complete and accurate progress reports at regular intervals, and at least yearly, to all reviewing IRBs. In the case of a significant risk device (as is your device), you shall also submit progress reports to the FDA. Should you terminate or complete the study, you are also obligated to notify the FDA and your IRB within 30 days of termination or completion.

You have failed to adhere to the above-stated regulations in that you did not submit progress reports to FDA for 2010 and 2011. Failure to submit progress reports to the FDA limits the agency's ability to oversee the clinical study and properly review the progress and safety of the study.

In your response letter, pg. 9, Corrective action for Observation 7, you stated that you had incorrectly assumed that progress reports were no longer necessary because the study was no longer enrolling subjects. You sent a letter, dated February 24, 2012, to the FDA Document Mail Center explaining this situation, stating that you are now in the process of drafting the progress report. Please provide us with an update on the status of this progress report and an expected completion date.

We also noticed that the monitoring plan in your IRB-approved protocol indicates that the DSMC will evaluate the progress of interventions, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome. However, the DSMC did not ensure data quality in that it did not identify the numerous record deficiencies that the FDA Investigator observed during this inspection. In your response, pg. 9, Corrective action for Observation 8i, ii, and iii, you stated that you plan to expand the DSMC responsibilities to **(b)(6)**. Please provide us with a complete monitoring plan including your proposed expanded procedures for monitoring.

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-investigator to ensure compliance with the Act and applicable regulations.

Within 15 working days of receiving this letter, please provide documentation of the actions that you have taken or will take to correct the violation 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 action.

Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you, including initiation of disqualification proceedings against you in accordance with 21 CFR 812.119.

Your response should reference "CTS # G070098/E001" and be sent to:

Attention: Kathy Weil
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3566

Silver Spring, Maryland 20993-0002

A copy of this letter has been sent to FDA's Denver District Office, Bldg. 20, Denver Federal Center, P.O. Box 25087, Denver, CO 80225. Please send a copy of your response to that office as well.

We believe that a teleconference would be helpful to further discuss the observations, any CAPA you have or plan on implementing, and answer any questions you may have. Please contact Adam Donat at Adam.Donat@fda.hhs.gov within 2 weeks of receiving this letter with several possible dates and times for this teleconference. We will ask that you take meeting minutes and provide us with a copy.

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 [1].

You will find information to assist you in understanding your responsibilities and planning your corrective action 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/ [2].

If you have any questions, please contact Adam Donat at our main number (301) 796-5490, directly at (301) 796-5316, or by email at Adam.Donat@fda.hhs.gov.

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

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1. http://www.fda.gov/Training/CDRHLearn/ucm162015.htm
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