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ADVANCED MAGNETIC RESEARCH INSTITUTE

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Food & Drug Administration
Center for Devices & Radiological Health, Office of Compliance
Division of Bioresearch Monitoring, Program Enforcement Branch (HFZ-312)
2094 Gaither Road
Rockville, MD 20850

ATTN: Viola Sellman, Chief, Program Enforcement Branch

Re: Warning Letter to Trent Nichols, M.D., AMRI-PA
Received from:
Timothy A. Ulatowski, Director
Office of Compliance, Center for Devices & Radiological Health

Dear Ms. Sellman,

This is a letter of response documenting the specific steps being taken to address the violations noted in the Warning Letter dated February 24, 2005.

An inspection of the Advanced Magnetic Research Institute (AMRI) in Hanover, PA was conducted by Ms. Susan Laska of the FDA's Philadelphia District Office from November 16 through November 22, 2004. The following deviations were noted on Form FDA 483 and reviewed in the Warning Letter:

1. Failure to provide adequate informed consent.
    a. The document in use failed to address the following required elements:
        i. Explanation of alternative procedures that may be advantageous to the subjects.
        ii. A description of any foreseeable risks or discomforts to the subjects.
        iii. A description of any benefits to the subjects that be reasonably expected from the research.
    b. There is no documentation to show that the informed consent form used in the study during the period of 2003 and 2004 was IRB reviewed and approved.
    c. Study subjects were not provided with a copy of the informed consent form.

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2. Failure to ensure that the investigation is conducted according to the signed agreement, the investigational plan, applicable FDA regulations and any conditions imposed by the IRB.

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a. Diagnostic tests were not completed as specified in the protocol which is part of the investigational plan. The MME protocol for Diabetic Peripheral Neuropathy specifies nerve conduction testing by Neurometer for subjects in the study; this was not performed.
b. Forms required by the protocol including the Initial Contact Form, Demographic Form, Exclusion Form, Pre-treatment Check Sheet, Session Check Time Form and Disease Specific Questionnaire were not found in any of the charts reviewed.
c. Records were reviewed that showed 3 subjects that were treated with the device but provided no documentation that they were seen and evaluated by Dr. Nichols.

3. Failure to maintain accurate, complete and current records relating to the investigator's participation in the investigation.
   a. Lack of a file including IRB correspondence regarding protocol approval, informed consent, advertisements and periodic reports.

4. Concern was noted regarding participation as a voting member on the IRB that reviewed the MME studies from 1/21/1999 through 2/7/2004. This was noted in the letter by Timothy Ulatowski and was not part of the Investigational Observations by Ms Laska.

The following action is being taken or has been taken in regard to the issues listed above:

1. (a) (i) The Informed Consent Form has been revised to address the deficiencies that were listed. This form received IRB approval in January 2005. Please see the attached revised form (Appendix A). Because feasibility studies are being conducted for a number of disease conditions, the areas of the form that address specific alternative treatments are presented as a blank space to be filled in as appropriate to the disease condition.

(ii) The MME has been previously determined to be a non-significant risk device. The minor discomforts that have been reported with MME use thus far have been listed in the revised document (Appendix A).

(iii) A description of the possible benefits to the subjects from participation in MME research has been added to the revised document (Appendix A).

1. (b) A master file containing all IRB correspondence and approval of protocols and forms is being updated. The current informed consent form has been IRB approved.

1. (c) All study participants will have a copy of the Informed Consent given to them. A memo has been distributed to all AMRI staff regarding the procedures for providing informed consent and proper documentation required (Appendix B).

2. (a) I believe there was a misunderstanding regarding the stage of our investigations at the time Ms. Laska conducted her inspection at this site, November 16 – 22, 2004. The Phase 3 Study on Diabetic Peripheral Neuropathy was not yet started, as adjustments are still being made to the protocol. Our work at that time was still Phase 2 dosimetry in an effort to determine optimal length of treatment time. We will be starting the Phase 3 protocol and study this spring 2005 and can assure you that all subjects will be evaluated and treated according to the protocol.

In regard to diagnostic testing of subjects treated for other disease conditions, our protocol notes that "preliminary diagnostic tests include standard clinical tests appropriate to the condition under review". In my clinic medical charts which are separate from the AMRI MME charts, I have documented medical testing as appropriate to the disease conditions being treated. A treatment summary form will be included in the AMRI MME chart to document and summarize the assessments that are done for each subject and their condition under treatment.

2. (b) The Initial Contact Form, Exclusion Form, Demographic Form, Pre-treatment Check Sheet and Disease Specific Questionnaire will be maintained in the subjects files from now on. A memo has been sent to all AMRI employees reviewing the required forms that must be included in the MME charts (Appendix C). The MME Session Check Time Form is not being used at any of the AMRI clinics and has been removed from the

clinic protocol. In its place is Symptom Tracking Form that is used to track symptom response, treatment exposure times and adverse reactions or other pertinent observations.

2. (c) Clearly, a preliminary medical evaluation is necessary before treatment begins. The 3 patients in question were later found to have medical records with complete history and physical exams that had been filed in our storage department located in the rear of the office and were inadvertently missed during the inspection. They were members of the staff personnel families.
I will be careful to comply and ensure the final evaluations have been completed and documented before and after all treatments. My staff will be notified to be certain that documentation of these evaluations will be present in the chart prior to the subjects receiving MME treatment (Appendix C).

3. (a) I have taken steps to update my IRB files to be certain that the proper forms for Protocols, Informed Consent, Periodic Reports and Advertisements for Patients are approved and on hand.

4. Re: Conflict of Interest in IRB. I was elected Chairman of the Advanced Magnetic Research Institute International's IRB on January 2, 1999, as stated, but did not become an Investigator until February 10, 2000, starting pilot studies on February 15, 2000. At that time Ronald Lawrence, M.D., PhD., accepted the position of AMRI IRB Chairman. This action was confirmed at the next annual IRB meeting, January 28, 2001. I was not removed from the board until the summer of 2004 and was notified by letter. During the years of 2002, '03, and '04, I was retained due to my previous research experience in contributing to the development of new protocols in treatment, so was performing in that capacity only. Your observation is obviously valid regarding approving one's own internal research. All individuals with possible conflict of interest were removed from the AMRI IRB at that same time in 2004, preparatory to starting the Phase 3 Studies on Diabetic Neuropathy.

I trust this addresses your concerns satisfactorily.

Yours truly,

Trent Nichols, M.D

CC:

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