DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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October 10, 2001

Michael Rosenblatt, M.D.
President
Beth Israel Deaconess Medical Center
330 Brookline Avenue
Boston, MA 02215

RE: Human Research Subject Protections Under the Multiple Project Assurance (MPA) M-1544
Research Project: Grant # 1R01MH57980-01A1–"Transcranial Magnetic Stimulation (rTMS) in Depression
Principal Investigator: **Alvaro Pascual-Leone, M.D., Ph.D.**

Dear Dr. Rosenblatt:

The Office for Human Research Protections (OHRP) has reviewed the Beth Israel Deaconess Medical Center (BIDMC) September 6, 2001 report regarding the above referenced matter.

Based upon its review, OHRP makes the following determinations:

(1) Department of Health and Human Service (HHS) regulations at 45 CFR 46.102(d) define research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. HHS regulations at 45 CFR 46.102(f) define a human subject as a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. HHS regulations at 45 CFR 46.116 stipulate that no investigator may involve a human being as a subject in research covered by the regulations, unless the investigator has obtained legally effective informed consent of the subject or the subject's legally authorized representative, unless this requirement has been waived in accordance with 45 CFR 46.116(c) or (d). Finally, HHS regulations at 45 CFR 46.177(a) stipulate that informed consent be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative.

Based upon the following information, OHRP finds that human subject research was initiated under the above referenced protocol without the investigator obtaining and documenting the legally effective informed consent of the subjects:

(a) OHRP finds that the procedures for withdrawing subjects from medications and for screening potential subjects for determination of eligibility for the research constituted human subjects research activities.

(b) Twenty one subjects were withdrawn from medications prior to signing informed consent documents. OHRP acknowledges that the investigators felt this was necessary so that the subjects could undergo withdrawal under the supervision of their local physician. Nevertheless, research-related interventions may not be conducted prior to the investigator obtaining and documenting the legally effective informed consent subject or their legally authorized representative.

(c) Three of these subjects had baseline evaluations and drug withdrawal prior to signing informed consent documents.

(d) The complainant, CH received research-related interventions (a detailed neurological exam, detailed medical history, and Hamilton Depression rating) on July 27, 1998, without signing an informed consent document for the study. A July 27, 1998 letter from the Principal Investigator to the subject's physician stated, "[t]hank you very much for referring you patient, [CH], to our Behavioral Neurology Clinic for consultation on his possible suitability for our ongoing trial of Transcranial Magnetic Stimulation (TMS) in depression. I had the pleasure of seeing him today, completed a detailed neurological exam, reviewed the history with the patient....[CH's] Hamilton Depression rating score today was [x]...."

Action 1– Required: By November 21, 2001, please provide OHRP with appropriate corrective action plan to ensure that research-related interventions are not conducted prior to the investigator obtaining and documenting legally-effective informed consent in accordance with, and to the extent required, by HHS regulations at 45 CFR 46.116 and 46.117.

(2) OHRP finds that the informed consent documents reviewed and approved by the Institutional Review Board (IRB) for this study failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a): A description of the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental. The informed consent document failed to include the following information:

(i) Prior to the rTMS intervention, if the subject is on medication, that the medication will be withdrawn from the subject for a period lasting from two to four weeks, depending on the type of medication.

(ii) A description of the neurologic, neuropsychologic, neurophysiologic, and neuroradiologic tests to be conducted, and the schedule for these tests following the rTMS intervention, including the performance of electroencephalograms.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts. The risks and discomforts of the medication withdrawal and of the neurologic, neuropsychologic, neurophysiologic, and neuroradiologic tests to be conducted, and performance of electroencephalograms were not included in the informed consent document.

(3) HHS regulations at 45 CFR 46.116 require that the information that is given to subjects must be in language understandable to the subject. OHRP finds that the informed consent document approved by the IRB for this study appeared to include complex language that would not be understandable to all subjects.

Action 2– Required: OHRP acknowledges that the IRB has asked the Principal Investigator to revise the informed consent document. By November 21, 2001 please provide OHRP a copy of the revised document after it has been reviewed and approved by the IRB. Please also provide OHRP with an analysis by the IRB of any need to re-contact subjects to provide additional appropriate information regarding their participation in the research.

(4) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that the following protocol changes were implemented without IRB approval:

(a) The IRB application referenced the fMRI as the neuroradiologic test that will be performed on the subject. After NIH peer review the investigators decided not to conduct the fMRI.

(b) The IRB application stated that 200 subjects with major depressive disorder (MDD) will be studied over a five year period. The number of subjects was changed after NIH peer review to study 40 normal volunteers and 80 patients with MDD over four years.

Action 3– Required: By November 21, 2001 please provide OHRP with appropriate corrective action plan to ensure that proposed changes in a research activity are not implemented prior to IRB review and approval.
(5) HHS regulations at 45 CFR 46.115 (a)(2) require that the minutes of IRB meetings

document the vote on IRB actions including the number of members voting for against, and abstaining. OHRP finds that prior to March 2000, no votes were recorded in the minutes of IRB meetings regarding continuing review of research.

(6) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

OHRP finds that continuing review of research by the IRB does not appear to be substantive and meaningful.

Action 4– Required: OHRP acknowledges that the IRB has recently changed its method of recording votes and conducting continuing review. By November 21, 2001 please provide OHRP with copies of the minutes from the last 3 IRB meetings.

(7) OHRP is concerned that there may have been inadequate provisions, with respect to the complainant, to protect his privacy regarding his participation in the research, as required by HHS regulations at 45 CFR 46.111(a)(7).

Corrective Action: OHRP acknowledges that the Lab for Magnetic Brain Stimulation has changed its policies and procedures, including removing the name of the lab from patient-related correspondence, not leaving voice-mail messages identifying themselves as healthcare providers, and proper authorization allowing for heathcare provider communication. OHRP finds that these corrective actions are appropriate.

OHRP has the following additional concern.

(8) Your September 6, 2001 report included numerous documents that were sent to prospective subjects and their physicians, including an initial information letter to patients, information packets to physicians and to patients, a recruitment letter to physicians, initial information letter to physicians, acceptance letter to prospective subjects, an appointment confirmation letter to prospective subjects, a denial letter and a thank you letter to subjects.

OHRP is concerned that this appears to be no evidence that the IRB reviewed and approved these materials. Please respond. In your response, please provide the dates of review and approval of these materials, if any.

Please provide your response to the above determinations and concern so that OHRP receives it no later than November 21, 2001. If upon further review of the concerns and questions, BIDMC identifies instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance. **Please note OHRP's new address.**

OHRP appreciates the commitment of your institution to the protection of human subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc Dr. Alan Lisbon, Chair, BIDMC IRBs
Dr. Alvaro Pascual-Leone, BIDMC
Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Mr. George Gasparis, OHRP
Ms. Freda Yoder, OHRP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA