DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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April 30, 2002

Paul Levy
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 Mr. Levy:

The Office for Human Research Protections (OHRP) has reviewed the Beth Israel Deaconess Medical Center (BIDMC) April 24, 2002 report regarding the above referenced matter.

Based upon its review of previous reports, OHRP made the following determinations regarding the above-referenced research:

> (1) In its October 10, 2001 letter to BIDMC, OHRP found 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.
> OHRP requested appropriate corrective action plans to ensure that no research-related interventions are conducted by any BIDMC investigator 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.
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> **Corrective Actions:** OHRP acknowledges that these requirements have been published in the

BIDMC Clinical Trials Newsletter, have been included in the IRB application form, and are outlined in the draft IRB Policy and Procedure Manual. OHRP finds that these corrective actions are adequate to the address the above finding and are appropriate under the BIDMC MPA.

(2) OHRP found that the principal investigator made and implemented changes to the protocol prior to review and approval by the IRB.

Corrective Actions: OHRP acknowledges that the BIDMC IRB suspended all of Dr. Pascual-Leone's protocols pending resolution of this matter. The IRB has instituted an Intensive Monitoring Period for this investigator, which includes provision to the IRB of enrollment information, including dates, of every subject enrolled in the research for the first six months after lifting the suspension. In addition, the principal investigator may not submit additional studies to the IRB during that time.

OHRP also acknowledges that the principal investigator has hired a new administrative coordinator for the laboratory who is experienced in administrating clinical trials and who has received training in human subject protections. In addition, the laboratory has developed a database to track protocols and all subject interactions to ensure that subjects are eligible and do not undergo research interventions prior to giving informed consent. The principle investigator is now conducting the clinical trial as approved by the IRB and has submitted a new protocol for the additional interventions. The laboratory has instituted internal audits of all active studies at least monthly and will consult with an outside auditor to conduct additional audits periodically. OHRP finds that these corrective actions are adequate to the address the above finding and are appropriate under the BIDMC MPA.

As a result, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

OHRP provides the following additional guidance:

(3) OHRP again notes that when the convened IRB requests substantive clarifications or modifications that would be necessary for the IRB to make the required findings at 45 CFR 46.111, IRB approval of the proposed research should be **deferred**, pending subsequent review by the convened IRB of responsive material. Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

(4) OHRP notes that suspensions or terminations of IRB approval must be reported to OHRP as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). As BIDMC acknowledges, if the IRB does not re-approve the research by the specified expiration date

subject accrual should be suspended pending re-approval of the research by the IRB. Enrollment of new subjects cannot ordinarily occur after the expiration of IRB approval. BIDMC is correct in stating that such expirations need not be reported to OHRP. However, if a routine audit reveals evidence of non-compliance and the IRB suspends enrollment of new subjects until the matter can be resolved, OHRP would expect such a suspension to be reported to OHRP.

(5) The BIDMC written IRB policies and procedures should be expanded to provide the operational details for each of the following procedures required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4) and (5):

> (i) The procedures which the Institutional Review Board (IRB) will follow for conducting its initial review of research.
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> (ii) The procedures which the IRB will follow for conducting its continuing review of research.
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> (iii) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.
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> (iv) The procedures which the IRB will follow for determining which projects require review more often than annually.
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> (v) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.
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> (vi) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
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> (vii) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, anyDepartment or Agency head, and OHRP of (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

For additional guidance, visit our website at
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/wirbproc.pdf

(6) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* or proposal for research covered by the assurance has been reviewed and approved by the IRB.

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. Yvonne Higgins, OHRP
Mr. Barry Bowman, OHRP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA