DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 30, 2002

Bruce M. Cohen, M.D., Ph.D.
President and Psychiatrist in Chief
McLean Hospital
115 Mill Street
Belmont, Massachusetts 02478-9106

**RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1287**

**Journal Publication: Popper CW. Do Vitamins or minerals (apart from lithium) have mood-stabilizing effects? J Clin Psychiatry. 2001;62:933-3512.**

Dear Dr. Cohen:

The Office for Human Research Protections (OHRP) has reviewed your April 17, 2002 report responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) that were presented in OHRP's March 18, 2002 letter regarding the above-referenced publication.

The allegations involved the following:

(1) The activities described in the above-referenced publication involved human subject research, and the author failed to obtain (a) Institutional Review Board (IRB) review and approval of the research, as required by HHS regulations at 45 CFR 46.109(a); and (b) the legally effective informed consent of the subjects, as required by HHS regulations at 45 CFR 46.116.

(2) The investigator for the above-referenced activity failed to ensure that risks to subjects were minimized by using procedures consistent with sound research design, as required by HHS

regulations at 45 CFR 46.111(a)(1).

(3) The investigator for the above-referenced activity failed to maintain the confidentiality of the data, as required by HHS regulations at 45 CFR 46.111(a)(7).

Based upon its review of your report, OHRP finds no evidence to substantiate the above allegations. In particular, OHRP acknowledges your statements that (i) the author of the above-referenced publication did not systematically collect data or test and evaluate EM PowerPlus in a way designed to contribute to generalizable knowledge; (ii) EM PowerPlus was given to patients as part of the author's clinical practice; and (iii) as a result, the activities described in the above-referenced publication did not constitute research as defined by HHS regulations at 45 CFR 46.102(2) and did not require IRB review and approval.

As a result of the above determination, 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.

At this time, OHRP provides the following additional guidance regarding the written IRB procedures provided with your report:

(1) In conducting the initial review of proposed research, IRBs must obtain information in sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111. Materials should include the full protocol, a proposed informed consent document, *any relevant grant application(s), the investigator's brochure (if one exists),* and any recruitment materials, including advertisements intended to be seen or heard by potential subjects. The written IRB procedures should indicate that investigators are required to submit any relevant grant applications and investigator's brochure

(2) If the IRB uses a primary reviewer system, the primary reviewer(s) should do an in-depth review of all pertinent documentation (see previous paragraph). All other IRB members should at least receive and review a protocol summary (of sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111), the proposed informed consent document, and any recruitment materials, including advertisements intended to be seen or heard by potential subjects. In addition, the complete documentation should be available to all members for review.

(3) Written IRB procedures should include lists of specific documents distributed to primary reviewers (if applicable) and to all other IRB members for initial review, continuing review, review of protocol changes, and review of reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(4) The last paragraph on page 6 describes a procedure where the Administrative Coordinator of the Human Subjects Program (HSP) "will review changes that are simple and routine to ensure that the investigator has made the modifications required by the IRB" for protocols with "Approval Pending." Please note that unless the HSP Administrative Coordinator is also a voting member of the IRB, the modifications required by the IRB as a condition of approval should also be reviewed by the IRB Chair or a member designated by the Chair.

(5) 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 (i) the number of subjects accrued; (ii) a summary 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 since the last IRB review; (iii) a summary of any relevant recent literature, findings obtained thus far, amendments or modifications to the research since the last review, any relevant multi-center trial reports, and any other relevant information, especially information about risks associated with the research; and (iv) 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 OHRP guidance at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm).
Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

(6) The written procedure for continuing review should indicate whether a primary reviewer system is used.

(7) The written procedures should be expanded to include a specific procedure for how the IRB determines which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review, including specific criteria used to make these determinations (e.g., such criteria could include some or all of the following: (i) randomly selected projects; (ii) complex projects involving unusual levels or types of risk to subjects; (iii) projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB; and (iv) projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other

sources).

(8) Regarding the procedure for obtaining Certificates of Confidentiality on page 25, please note that OHRP does not issue such certificates. Appropriate contact information for obtaining these certificates can be found at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/cert-con.htm.

(9) HHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval (see 45 CFR 46.103(b) and 46.116(f) and OHRP guidance at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc91-01.htm). When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration (FDA) requirements must be satisfied.

(10) Nothing in the HHS regulations at 45 CFR Part 46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law. However, when emergency medical care is initiated without the physician obtaining and documenting the legally effective informed consent of the patient or the patient's legally authorized representative for participation in research (unless the IRB has appropriately waived such requirements or found that the research is consistent with the Secretary's waiver for emergency research, see OPRR Reports, 97-01 at URL http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc97-01.htm), the patient may not be considered a research subject. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration requirements must be satisfied.

(11) Regarding the policy for pregnant women, fetuses, and in vitro fertilization on pages 43-44, please note that a revised Subpart B of 45 CFR Part 46 was issued on December 13, 2002 (see http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm).

(12) Regarding the informed consent document templates included with the written IRB procedures, the template should be modified to include:

> (a) A statement that participation is voluntary, refusal to participate will involve *no penalty or loss of benefits* to which the subject is otherwise entitled, and the subject may discontinue participation at any time *without penalty or loss of benefits* to which the subject is otherwise entitled.

(b) An explanation of whom to contact for answers to pertinent questions about *research subjects' rights.*

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

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. James I. Hudson, Chairperson, IRB-01, McLean Hospital
Dr. Scott E. Lukas, Chairperson, IRB-02, McLean Hospital
Dr. Charles W. Popper, McLean Hospital
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. George Gasparis, OHRP
Dr. Jeffrey Cohen, OHRP
Ms. Yvonne Higgins, OHRP
Mr. Barry Bowman, OHRP