DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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July 12, 2001

Michael F. Collins, M.D.
President
St. Elizabeth's Medical Center of Boston
736 Cambridge Street
Boston, MA 02135

RE: Human Subject Research Protections Under Multiple Project Assurance (MPA) M-1350

Research Activities: Gene Therapy Research Protocols
Principal Investigator: Dr. Jeffrey Isner

Dear Dr. Collins:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed the February 28, 2000 and August 2, 2000 reports from St. Elizabeth's Medical Center (SEMC) relating to clinical studies conducted by Dr. Jeffrey Isner and SEMC's system for the protection of human subjects. OHRP notes the following:

(1) OHRP acknowledges the investigation performed by SEMC regarding the reporting of serious adverse events related to the studies conducted by Dr. Isner. Additionally, OHRP acknowledges SEMC's commitment to implement the recommendations of SEMC's outside legal and medical counsel which were made as part of your February 28, 2000 report. These recommendations include:

(a) Enhancement of the responsibilities of the Institutional Review Board (IRB) especially with respect to reviewing and reporting of adverse events.

(b) Development of a training program for all investigators and IRB members relating to reporting of adverse events.

(c) Updating of all adverse events associated with all ongoing research involving gene therapy by Dr. Isner.

(d) Simplification of the documentation of IRB policies and procedures.

(e) Commitment of adequate administrative resources to the IRB to enable it to fulfill its responsibilities.

Action 1 - Required: By August 31, 2001, SEMC please provide to OHRP a progress report regarding the status of the implementation of the above recommendations.

Based upon its review of your reports, OHRP has made the following determinations regarding protection of human subjects at the SEMC:

(2) OHRP notes that the following protocols were apparently approved via an expedited review procedure prior to their approval by the full SEMC IRB:

Protocol #	Date of Expedited Review and Approval	Date of Full IRB Review
1296GI00	January 3, 1997	February 13, 1997
0797GI00	June 19, 1997	July 14, 1997
01980000	January 26, 1998	February 23, 1998
0599BI00	May 6, 1999	May 17, 1999

Each of these protocols involved the use of vascular endothelial growth factor gene therapy for myocardial angiogenesis. OHRP notes that the intervention involved (i.e., gene transfer) and the techniques employed in these protocols (e.g., cardiac catheterization, mini left anterior thoracotomy, intramyocardial injections) are clearly greater than minimal risk interventions.

HHS regulations at 45 CFR 46.110(b) limit the use of expedited review procedures to (1) specific research categories published which are published in the Federal Register and found to involve no more than minimal risk and (2) minor changes in previously approved research during the period for which approval is authorized. OHRP finds that the use of expedited review by the SEMC IRB to approve the above referenced protocols was not appropriate.

It appears that no subjects were enrolled in these protocols between the times when the protocols were given expedited approval and their full SEMC IRB approval, although OHRP cannot verify this for two subjects who were enrolled in protocol # 1296GI00, as is noted on the annual review form submitted by Dr. Isner dated May 8, 1997. These two subjects were apparently not included in the list of subjects provided by SEMC. Please provide the dates these subjects were enrolled in this protocol.

(3) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of

minor changes to previously approved research. OHRP finds that the SEMC IRB employed expedited procedures to review the following changes that exceed the limits of a minor change:

(a) An amendment of protocol # 06940000 on June 17, 1996 which was followed by a full SEMC IRB approval on July 8, 1996. This amendment involved a change in the introduction of the gene therapy vector from intra-arterial administration via angioplasty balloon to intramuscular injection.

(b) An expedited review was granted for an amendment to protocol # 0299VGI0 on April 21, 1999 involving the inclusion of subjects in a long term follow-up protocol. This amendment was approved by the full SEMC IRB on May 17, 1999.

(4) HHS regulations at 45 CFR 46.108 require that, except when an expedited review procedure is used, the IRB review proposed research at convened meetings at which a majority of the members of the IRB are present. OHRP finds that the IRB failed to meet this requirement for the SEMC IRB meetings held on February 22, 1999 (7 of 17 members present) and August 16, 1999 (6 of 18 members present). Thus, any actions taken at these meeting must be considered invalid. OHRP emphasizes that should the quorum fail during a meeting (e.g., those with conflicts being excused, early departures, loss of a nonscientist), the IRB may not take further action or votes until the quorum can be restored.

<u>Action 2 - Required</u>: By August 31, 2001, SEMC must submit to OHRP (i) a detailed corrective action plan to address findings (2) through (4) above; and (ii) a detailed plan for ensuring that all IRB members and staff, and all research investigators, are appropriately educated, on an ongoing basis, about the ethical principles and regulatory requirements for the protection of human subjects.

(5) OHRP finds that SEMC does not have adequate written IRB policies and procedures that describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) 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.

(b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head of (i) any unanticipated

problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

Action 3 - Required: By August 31, 2001, the SEMC must submit to OHRP revised written IRB policies and procedures that adequately describe the operational details of all activities stipulated by HHS regulations at 45 CFR 46.103(b)(4) and (5).

At this time OHRP has the following additional questions and guidance:

(6) OHRP has received a copy of a Food and Drug Administration (FDA) warning letter, dated April 28, 2000, regarding possible noncompliance with FDA regulations involving Dr. Isner's gene therapy protocols. A portion of SEMC's August 2, 2000 report to OHRP appears to be an excerpt of a response to FDA's warning letter. OHRP is concerned that the allegations presented in the FDA warning letter represent serious noncompliance which might also be reportable to OHRP. Please respond. In your response please include a copy of all correspondence between FDA and SEMC regarding this warning letter.

(7) OHRP is concerned that the IRB approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research should be deferred, pending subsequent review by the convened IRB of responsive material. (b) 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. Please respond.

(8) Regarding the SEMC Research/ Human Subjects Committee (IRB) Administration Policies and Procedures (Binder 1, Section B):

(a) The definition of Application on page 056 states, "Most of the committee members will not receive a copy of the study protocol, so it's important that the completed application is comprehensive enough to allow for an adequate review."

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 applications, the investigator's brochure (if one exists), and any advertising intended to be seen or heard by potential subjects. Unless a primary reviewer system is used, all members should receive a copy of the complete documentation. These materials

should be received by members sufficiently in advance of the meeting date to allow review of this material.

If the IRB uses a primary reviewer system, the primary reviewer(s) should do an in-depth review of all pertinent documentation (see (14) above). 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 advertising material. In addition, the complete documentation should be available to all members for review.

(b) Compassionate use is defined on page 056 as "Emergency use of a test article." The procedures go on to state: "If there is not sufficient time to obtain IRB approval before treatment, the investigator should obtain informed consent from the subject, provide the study treatment, and report the incident to the IRB in writing within five working days."

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), 46.116(f) and OPRR Reports 91-01). 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 research activity. When emergency care involves investigational drugs, devices, or biologics, FDA requirements must be satisfied

(c) On page 061 under "Approval Process for Human Research Investigators," section II, point B states: "To outline instructions for securing expedited approval of Human Research Protocols in those cases wherein there is documentary evidence that normal processing through pre-established channels would cause undue problems."

As was noted above, HHS regulations at 45 CFR 46.110(b) limit the use of expedited review procedures to:

> (i) Specific research categories published in the Federal Register at 63 FR 60364.
>
> (ii) Review of minor changes to previously approved research.

OHRP recommends that documentation for initial and continuing reviews conducted utilizing expedited review procedures include the specific permissible

categories (see 63 FR 60364) justifying the expedited review. Additionally, OHRP recommends that SEMC adopt written policies describing the types of minor changes in previously approved research which can be approved by expedited review in accordance with HHS regulations at 45 CFR 46.110(b)(2).

(d) On page 062, subsection C, point 3 states: "[Chairman of the Committee] Refers minutes of Research /Human Subjects Committee to the Board of Trustees, who have absolute veto power over any previous decision."

HHS regulations at 45 CFR 46.112 stipulates that research approved by an IRB may be subject to further review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB. OHRP is concerned that the use of a veto by the Board of Trustees in such a situation may violate HHS regulations at 45 CFR 46.112, as well as the SEMC MPA, if the Board of Trustees can approve research disapproved by the IRB. Please respond.

(e) On page 073 under "Alternative IRB Committee Members" it states: "For IRB purposes only, the entire SEMC staff may be considered to be alternative IRB Committee Members." OHRP is concerned that all of the SEMC staff would not make appropriate alternate IRB members. For example replacement of an IRB member with one whose primary interests are non-scientific may not be appropriate under certain circumstances. Alternate IRB committee members should be included on the IRB membership roster submitted to OHRP. Please respond.

(f) On page 075, Section 1 states: "Send a copy of the application, consent form and protocol along with a cover memo to a primary reviewer of your choice." The new application should be reviewed by reviewers of sufficient expertise in the area of research. If individuals with appropriate expertise are not members of the IRB, appropriate consultants need to be identified.

(g) On page 076, Section 8 states: "If the investigator is in a hurry (and investigators usually are when it comes to advertisements) ask the chair to give the ad an expedited review." OHRP is concerned that this may be an inappropriate use of the expedited review particularly if the advertisement is part of a new protocol submission. When 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 applications, the investigator's brochure (if one exists), and any advertising intended to be seen or heard by potential subjects. Unless a primary reviewer system is used, all members should receive a copy of the complete

documentation. These materials should be received by members sufficiently in advance of the meeting date to allow review of this material.

Please submit your response to the above questions and concerns to OHRP by August 31, 2001

OHRP appreciates the commitment of your institution to the protection of human subjects of research. Please contact me if you have any questions regarding this matter.

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Alan B. Ashare, Chair SEMC IRB
Dr. Jeffrey Isner, Principal Investigator, SEMC
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Mr. Barry Bowman, OHRP
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