DEPARTMENT OF HEALTH & HUMAN SERVICES

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Jeffrey M. Cohen, Ph.D.
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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1185 and Federalwide Assurance (FWA) 93

Research Project:	**Cytokines and Extracellular Matrix in Bronchopulmonary Dysplasia (Protocol # 0199-520)**
Principal Investigators:	**Dr. Zubair Aghai, Dr. Harmut Hanauske-Abel, and Dr. Alfred Krauss**
Research Project:	**Effects of Diurnal Hormonal Changes on Matrix Metabolism (Protocol # 1296-629)**
Principal Investigator:	**Dr. Madeleine Harbison**
Research Project:	**Endocrine Function in Fanconi Anemia (Protocol # 0694-480)**
Principal Investigator:	**Dr. Michael Wajnrach**
Research Project:	**Hypo-Hyperadrenal States (Protocol # 0296-223)**
Principal Investigator:	**Dr. Maria New**

Research Project: **A Clinical Trial to Prevent the Complications of Insulin Resistance (Including Type II Diabetes) (Protocol # 0800-354)**

Principal Investigator: **Dr. Noel Maclaren**

Dear Dr. Cohen and Dr. Gotto:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of the human subject protections system at the Weill Medical College of Cornell University (WMC) on May 18 - 20, 2004. The evaluation, conducted by 7 OHRP staff and with the assistance of 3 expert consultants, included meetings with senior institutional officials, the chairperson of the Institutional Review Board (IRB), approximately 10 IRB members, IRB administrative staff, several research investigators, including four of the principal investigators for the above-referenced research projects, and the Chair of the Department of Pediatrics. The evaluation involved review of IRB files for over 35 protocols and minutes of the IRB meetings since 2000.

In the course of the OHRP review, the IRB chairperson, IRB members, and IRB administrative staff displayed a sincere commitment to the protection of human subjects. Furthermore, the volume of research reviewed and the amount of time and effort devoted to IRB activities by the IRB chairperson and staff indicate great dedication to the mission of the IRB. Investigators demonstrated a culture of respect for the IRB process. The IRB Administrator and staff were very helpful and accommodating to OHRP during the site visit.

Findings

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP's review of IRB documents reveals evidence that the IRB does not always make the required findings when reviewing research involving children, and when the findings are made, they are sometimes inappropriate (e.g. for protocol #0204-165, which involved a dose-finding, safety study of a drug in pediatric hypertensive patients, the IRB found that the protocol was approvable under HHS regulations at 45 CFR 46.404). Based on OHRP's discussions with the IRB chairperson and IRB members, OHRP is concerned that the IRB lacks a detailed understanding of HHS regulations at 45 CFR part 46, subpart D, which require specific IRB determinations related to the risks and potential benefits when children are involved as subjects of research.

(2) HHS regulations at 45 CFR 46.103(b) and 109(a) require that the IRB must review and approve all non-exempt human subject research covered by an assurance. OHRP finds that subjects were enrolled into protocol #0199-520 prior to IRB review and approval. OHRP notes that the initial approval of protocol #0199-520 occurred on March 15, 1999. However, the list of subjects for this protocol provided with the WMC report

to OHRP dated June 19, 2003 states that eleven subjects were enrolled in the study between June 15, 1998 and March 15, 1999.

(3) HHS regulations at 45 CFR 45.116 state that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. OHRP finds that the investigator initiated research without meeting this requirement for one subject in protocol #0296-223.

(4) HHS regulations at 45 CFR 46.117(a) require 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, unless the IRB waives this requirement. OHRP finds that WMC could provide no documentation of written consent for 20 subjects enrolled in protocol #0199-520. In addition, for protocol #0800-354 telephone consent was obtained for two subjects and one informed consent document was not signed. OHRP found no evidence that the IRB had waived the requirements for documentation of informed consent for these two protocols.

(5) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. OHRP finds that the minutes of IRB meetings often failed to meet these requirements. In specific, OHRP determined from reviewing minutes of IRB meetings and interviews with IRB staff that the discussion recorded in the minutes is copied from the IRB chairperson's letters to the investigators indicating changes to be made to the protocols and the informed consent documents, and therefore the minutes usually lacked a written summary of the discussion of controverted issues and their resolution. OHRP found several examples of changes suggested in reviewer sheets that were not mentioned in the minutes of the IRB meetings (e.g., protocol #0801-842, protocol #0503-840, and protocol #1202-623). In addition, it was not always clear from the minutes when IRB members leave the room, which may result in inaccuracies in the recorded vote count. This also may have affected maintenance of a quorum.

(6) HHS regulations at 45 CFR 46.115(b) require that IRB records be retained for at least 3 years, and records relating to research which is conducted be retained for at least 3 years after completion of the research. OHRP finds that for protocol #0199-520 and #0296-223, this requirement was not met.

(7) HHS regulations at 45 CFR 46.103(a) and (b)(5)(ii) require prompt reporting of any suspension or termination of research to appropriate institutional officials, the Department or Agency head and OHRP.

(a) OHRP finds that WMC IRB suspended protocol #0694-480 on November 13, 2000 and this suspension was not reported to OHRP.

(b) OHRP finds that the WMC IRB suspended protocols #0296-223 and #0800-354 in the fall of 2002 and these suspensions were not reported to OHRP until June 19, 2003.

(8) 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) For protocol #0296-223, subjects were enrolled outside the protocol age range prior to IRB review and approval of the amended protocol.

(b) Protocol #0800-354 stated that subjects would be randomized between metformin and placebo. During our interview, the investigator stated that, among other things, the protocol was changed to a single arm study without prior IRB review and approval.

(c) For protocol #0801-842, between August 12, 2002 and July 22, 2003, the protocol was changed from a double-blind study to a single blind study. OHRP could find no evidence of IRB review and approval of this protocol modification. Further, the continuing review form reviewed by the IRB on July 22, 2003 stated "no changes since last continuing review."

(9) OHRP finds that when reviewing protocol applications, the IRB often appears to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. OHRP notes that for non-sponsored studies the IRB only receives the Request for Approval of Investigation Involving Use of Human Subjects (IRB application) which contains the Non-technical Research Plan. For such projects the IRB appears to review only minimal information regarding (a) research design and procedures; (b) subject recruitment procedures; (c) procedures under which consent will be obtained and documented; (d) the equitable selection of subjects; (e) provisions for monitoring the data collected to ensure the safety of subjects; (f) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (g) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable. OHRP notes that while the IRB application solicits some of this information, the records show that insufficient details are submitted to the IRB that would allow a review of research in a manner sufficient to determine that the research meets the criteria under HHS regulations at 45 CFR 46.111.

(10) OHRP finds that certain informed consent documents reviewed and approved by the IRB between 2000 and 2004 failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116 (a):

(a) Section 46.116(a)(1): (i) an explanation of the purposes of the research (i.e., the informed consent document for protocol #0296-223 does not include a description of the purpose); and (ii) a complete description of the procedures to be followed, and identification of any procedures which are experimental (i.e., for protocol #1195-099, it was not clear from the informed consent document that in vitro fertilization (IVF) was part of the protocol).

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts. For example:

(i) For protocol #0801-842, the protocol included risks of death, rare central nervous system demyelinating disorders, and abdominal pain, but these risks were not included in the informed consent document.

(ii) For protocol #0503-840, the informed consent document did not list the risks of withdrawal of certain medications, including antidepressants and narcotics, prior to administration of the study drug, nor of cardiac changes due to the study drug.

(c) Section 46.116(a)(3): A description of any benefits to the subject or others that may *reasonably* be expected from the research. For protocol #0801-842, the informed consent included as a benefit, "...treatment with Etanercept will be free of charge." OHRP does not believe that receiving the study drug free of charge should be considered a potential benefit.

(d) Section 46.116(a)(4): A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. OHRP found that informed consent documents for multiple studies lacked this element. For example, in protocol #0296-223, the informed consent document did not state that the tests conducted for the protocol could be obtained outside of the research.

(11) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP is concerned that certain informed consent documents approved by the IRB include complex language that would not be understandable to all subjects. For example:

(a) For protocol #1195-099, the language throughout the informed consent document was extremely complex. For example, it stated "the physicians...wish to determine whether the autologous (your own) endometrial coculture cells

provide a more natural environment for early embryo development, which has been bypassed in IVF, resulting in preembryos of improved quality thus increasing your chances of pregnancy."

(b) For protocol #0702-342, the informed consent document included terms such "heart chamber communication" and "large communication" to describe holes in the heart, and "transthoracic echocardiogram" and "transesophogeal echocardiogram" without adequate definition.

(c) For protocol #0296-223, the language throughout the informed consent document was extremely complex. For example, it stated "metyrapone is a compound that interrupts cortisol production in the adrenal. Since cortisol is the feedback hormone to the pituitary, metyrapone administration tests pituitary adequacy in producing ACTH."

(d) For protocol # 0403-771, the informed consent document included terms such as "inhabitation of saliva" and "pulse steroid therapy" without adequate definition.

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

(a) The procedures which the IRB will follow for determining which projects require review more often than annually.

(b) 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.

(c) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department 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.

(13) HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. HHS regulations at 45 CFR 46.117(c) require specific findings on the part of the IRB for waiver of the usual requirements for the investigator to obtain a signed consent form from all subjects. OHRP finds no evidence that the IRB made the required findings when approving such waivers for protocol #1295-144.

OHRP notes that some of these same findings were made on July 3, 1996 following a site visit by the Office for Protection from Research Risks.

Questions and Concerns

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

(14) [Redacted]

(15) [Redacted]

(16) [Redacted]

(17) [Redacted]

OHRP Action

In view of the above determinations and in order to ensure adequate protections for human subjects, OHRP hereby restricts the WMC assurance (FWA 93), pending satisfactory completion of the required corrective actions described below.

Required Actions

(1) WMC must develop a satisfactory corrective action plan to address the above findings, and respond to the above questions and concerns. By June 30, 2004, please submit WMC's corrective action plan and response to OHRP's questions and concerns.

(2) WMC must re-review all ongoing research involving children covered by your FWA within the next six months. Research involving children may continue during the re-review period.

(3) WMC must provide quarterly progress reports to OHRP on the implementation of WMC's corrective action plan and the re-review of ongoing research involving children. The first progress report, due September 1, 2004, should include:

(a) A copy of the minutes of all IRB meetings convened since OHRP's site visit.

(b) A copy of any revised IRB written procedures.

(c) A list of all protocols involving children which have been re-reviewed by the IRB and the outcome of that review.

OHRP is available to assist WMC in the development and implementation of the corrective action plan. Furthermore, OHRP anticipates conducting a follow-up site visit within the next 9-12 months to assess the implementation of corrective actions.

Guidance

(1) HHS regulations at 45 CFR 46.116(a)(7) require the informed consent document to include an explanation of whom to contact for answers to pertinent questions about research subjects' rights (should include someone other than the investigator), and whom to contact in the event of a research-related injury to the subject. While a telephone number was usually provided for this purpose in the informed consent documents reviewed, OHRP recommends that a name or University office be included.

(2) OHRP recommends that documentation for initial and continuing reviews conducted under an expedited review procedure include: (a) the specific permissible categories (see 63 FR 60364-60367 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm) justifying the expedited review; and (b) documentation of the review and action taken by the IRB

chairperson or designated reviewer and any findings required under the HHS regulations.

(3) HHS regulations at 45 CFR 46.103(d) require that the adequacy of IRBs be evaluated in light of the anticipated scope of the institution's research activities, the types of subject populations likely to be involved, and the size and complexity of the institution. The regulations further require at 45 CFR 46.107(a) that IRBs be (a) sufficiently qualified through the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel; and (b) able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB administrator informed OHRP that the IRB relies on the investigator to provide the IRB with the local context when reviewing research conducted at foreign sites. Institutions have a profound responsibility to ensure that all IRBs designated under an OHRP-approved Assurance possess sufficient knowledge of the local research context to satisfy these requirements.

For detailed guidance on appropriate mechanisms for ensuring that the IRB has adequate knowledge of the local research context, please see:

http://ohrp.osophs.dhhs.gov/humansubjects/guidance/local.htm

(4) HHS regulations at 45 CFR 46.116(d) require that the IRB make and document four findings when approving a consent procedure which does not include, or which alters, some or all of the required elements of informed consent or when waiving the requirement to obtain informed consent. OHRP recommends that when approving such a waiver for research reviewed by the convened IRB, these findings be documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

Similarly, where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (b) approving research involving pregnant women, human fetuses, or neonates (see 45 CFR 46.204-207); (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP recommends that for research approved by the convened IRB, all required findings be fully documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

For research reviewed under an expedited review procedure, these findings should be documented by the IRB Chairperson or other designated reviewer elsewhere in the IRB record.

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

Sincerely,

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

cc: Mr. Jeffrey Lehman, President, Cornell University
Ms. Dorothy Hilpmann, IRB Administrator, WMC
Dr. David Behrman, Chairperson, IRB WMC
Dr. Maria New, WMC
Dr. Madeleine Harbison, WMC
Dr. Alfred Krauss, WMC
Dr. Noel Maclaren, WMC
Dr. Gerald Laughlin, WMC
Commissioner, FDA
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