DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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July 21, 2004

Antonio M. Gotto, Jr., M.D., D.Phil.
Provost for Medical Affairs and
Dean of the Medical College
Joan and Sanford I. Weill College of Medicine
of Cornell University
1300 York Avenue, Room F105
New York, NY 10021

Jeffrey M. Cohen, Ph.D.
Associate Dean
Joan and Sanford I. Weill College of Medicine
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1300 York Avenue, Box 5
New York, NY 10021

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. Gotto and Dr. Cohen:

The Office for Human Research Protections (OHRP) has reviewed the Weill Medical College of Cornell University's (WMC) June 29, 2004 letter, which was submitted in response to OHRP's letter of May 24, 2004.

In its May 24, 2004 letter, OHRP made the following findings:

(1) OHRP found that the WMC IRB failed to consistently make the determinations required under Department of Health and Human Services (HHS) regulations at 45 CFR 46.404-407. In addition, OHRP had concerns that the WMC IRB lacked a detailed understanding of the HHS regulations at 45 CFR part 46, subpart D.

Corrective Action: OHRP acknowledges that WMC IRB members and staff attended a training session on reviewing research involving children. The WMC report stated that it is also revising its IRB protocol form to include additional information relating to HHS regulations at 45 CFR 46, subpart B. OHRP believes that WMC meant to refer to subpart D when describing revisions to its IRB protocol form. Please clarify.

(2) OHRP found that subjects were enrolled in Protocol #0199-520 prior to IRB review and approval, as required by HHS regulations at 45 CFR 46.103(b) and 109(a).

(3) OHRP found that research was initiated on one subject enrolled in Protocol #0296-223 without obtaining legally effective informed consent from the subject or the subject's legally authorized representative, as required by HHS regulations at 45 CFR 46.116.

(4) OHRP found that the investigators for Protocol #0199-520 and #0800-354 failed to document consent by using a written consent form approved by the IRB, as required by HHS regulations at 45 CFR 46.117(a).

Corrective Action: OHRP acknowledges that WMC has terminated the studies noted in items (2)-(4). In addition, the entire Department of Pediatrics has participated in a training session concerning the protection of research subjects and IRB procedures and requirements. OHRP finds that these corrective actions adequately address the findings in items (2)-(4), above, and are appropriate under the WMC FWA.

(5) OHRP found that the minutes of IRB meetings failed to meet the requirements under HHS regulations at 45 CFR 46.115(a)(2). In addition, OHRP had concerns that IRB minutes may not have accurately reflected the vote count or maintenance of a quorum.

Corrective Action: OHRP acknowledges that WMC will generate minutes using a new database which has provisions for entering summaries of discussion into IRB meeting minutes. In addition, WMC has indicated that steps will be taken to ensure the appropriate documentation of attendance of IRB members at meetings. OHRP finds that these corrective actions adequately address the above finding, and are appropriate under the WMC FWA.

(6) OHRP found that IRB records and records relating to research for Protocol #0199-520 and #0296-223 were not maintained for at least three years after the completion of the research, as required by HHS regulations at 45 CFR 46.115(b).

Corrective Action: OHRP acknowledges that WMC will remind investigators in IRB approval letters of the requirement for retaining records. In addition, WMC has in place written procedures which address IRB retention of records. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the WMC FWA.

(7) OHRP found that the WMC failed to promptly report certain suspensions of research, as required by HHS regulations at 45 CFR 46.103(a) and (b)(5)(ii).

Corrective Action: OHRP acknowledges that WMC has revised its written IRB procedures to indicate that suspensions will be reported to the institutional official within 5 days and that the institutional official will promptly notify relevant federal agencies. In addition, a new computer database will generate copies of suspension letters for OHRP when the status of a protocol has changed to "suspended." OHRP finds that these corrective actions adequately address the above finding and are appropriate under the WMC FWA.

(8) OHRP found that protocol changes had been implemented without IRB approval, as required by HHS regulations at 45 CFR 46.103(b)(4)(iii).

Corrective Action: OHRP acknowledges that WMC reminds investigators in its letters of approval of the need to obtain IRB approval for all changes. WMC will emphasize this point as part of all future investigator education sessions. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the WMC FWA.

(9) OHRP found that the WMC IRB often lacked sufficient information to make the determinations required for approval under HHS regulations at 45 CFR 46.111.

Corrective Action: OHRP acknowledges that WMC has revised its IRB protocol application form which will now solicit additional information from investigators. In addition, WMC is revising its IRB reviewer checklist to help ensure that adequate information is present for approval. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the WMC FWA.

(10) OHRP found that certain informed consent documents failed to address particular elements of informed consent, as required by HHS regulations at 45 CFR 46.116(a).

Corrective Action: OHRP acknowledges that WMC has indicated that additional training will be provided to all IRB members on informed consent. In addition, informed consent will be an item included in training of investigators and staff. OHRP finds that these corrective actions fail to adequately address the above finding. In specific, these corrective actions do not include any actions taken to ensure that the informed consent documents for the protocols specified in OHRP's May 24, 2004 letter currently meet the requirements under HHS regulations at 45 CFR 46.116(a). Please respond.

(11) OHRP expressed concern that certain informed consent documents were not in language understandable to the subject or the subject's legally authorized representative, as required by HHS regulations at 45 CFR 46.116.

Corrective Action: OHRP acknowledges that WMC has indicated that additional training will be provided to all IRB members on this issue. In addition, this issue will be an item included in training of investigators and staff. OHRP finds that these corrective actions fail to adequately address the above finding. In specific, these corrective actions do not include any actions taken to ensure that the informed consent documents specified in OHRP's May 24, 2004 letter currently meet the requirements under HHS regulations at 45 CFR 45.116. Please respond

(12) OHRP found that the WMC IRB did not have written IRB procedures which adequately described certain activities, as required by HHS regulations at 45 FR 46.103(a) and (b)(4) and (5).

Corrective action: OHRP acknowledges that WMC has revised its written IRB procedures to address the activities noted in OHRP's May 24, 2004 letter. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the WMC FWA.

(13) OHRP found no evidence that the IRB made and documented the required findings for (i) the waiver of informed consent; or (ii) the waiver of the requirements for requiring the investigator to obtain a signed informed consent document for Protocol #1295-144, as required by HHS regulations at 45 CFR 46.116(d) and 46.117(c).

Corrective Action: OHRP acknowledges that WMC has indicated that additional training will be provided to all IRB members on the criteria for waiver of informed consent. OHRP finds that this corrective action fails to adequately address the above finding. In specific, this corrective action fails to include any actions taken to ensure that Protocol #1295-144 meets the requirements for waiver of informed consent or waiver of the requirement for use of a signed informed consent document. Please respond.

Additional Findings

(14) HHS regulations at 45 CFR 46.110(b)(2) permit the use of expedited review procedures for review of minor changes to previously approved research during the period for which approval is authorized. OHRP finds that the WMC IRB approved an amendment to the protocol entitled "Patient Preference in Primary Care/Depression Treatment" under expedited review procedures which exceeded this limitation.

Corrective Action: OHRP acknowledges that WMC has revised its written IRB procedures which include the development of standards for determining what constitutes a minor change in a research activity. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the WMC FWA.

(15) OHRP finds that WMC has adequately addressed the additional questions and concerns raised in OHRP's May 24, 2004 letter. However, OHRP requests that WMC provide a description of the progress made on verifying whether subjects were enrolled in Protocol #0296-223 without being provided an adequate description of the procedures to be followed.

Required Actions

OHRP reminds WMC that the restriction on its FWA remains in effect and that it must address the following required actions:

(1) By September 1, 2004, WMC must provide a corrective action plan which adequately addresses items (1), (10), (11), and (13), noted above.

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

(3) WMC must provide quarterly progress reports to OHRP on (i) the implementation of WMC's corrective action plans; (ii) the re-review of ongoing research involving children; and (iii) the progress made on verifying the status of subjects enrolled in Protocol #0296-223, as noted in item (15), above. The first progress report is due September 1, 2004.

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. Alfred Krauss, WMC
Dr. Noel Maclaren, WMC
Dr. Gerald Laughlin, WMC
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Ms. Shirley Hicks, OHRP
Ms. Janice Walden, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Melinda Hill, OHRP