DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 12, 2003

Arthur Rubenstein, MBBCh
Dean
Mount Sinai School of Medicine
One Gustave L. Levy Place
New York, NY 10029-6574

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1155

Research Project: A Double-Blind Controlled Trial of Nigral Grafting in Patients with Parkinson's Disease
Principal Investigator: C.W. Olanow, M.D.
Protocol Number: GCO 94-339 NE

Dear Dr. Rubenstein:

The Office for Human Research Protections (OHRP) has reviewed Mount Sinai School of Medicine's (MSSM's) February 28, 2001 report that was submitted in response to OHRP's December 11, 2000 letter to MSSM regarding the allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) involving the above-referenced research.

Based upon review of your February 28, 2001 report, OHRP makes the following determinations regarding the above-referenced research:

(1) HHS regulations at 45 CFR 46.111(a)(1) require that institutional review board (IRB) approval of research is based on the determination that risks to subjects are minimized. In particular, it was alleged that the IRB failed to minimize the risk of discomfort related to research-induced distress associated with the above-referenced research. Based on its review of information presented in your report, OHRP finds that this allegation was not substantiated. OHRP notes that as a result of your investigation in this matter, the MSSM IRB has established an ad hoc committee to attempt to define ways of educating investigators regarding the general need of making subjects aware of potential distress associated with study participation and, if possible, minimizing such distress during study participation.

(2) It was alleged that the informed consent document for the above-referenced study failed to disclose all reasonably foreseeable risks and additional costs to the subject that may have resulted from participation in the research, as required by HHS regulations at 45 CFR 46.116(a)(2) and (b)(3). Based on its review of information presented in your report, OHRP finds that this allegation was not substantiated.

(3) It was alleged that the informed consent document for the above-referenced study failed to accurately describe the timing of cross over to active intervention for subjects initially assigned to a placebo (operation without transplantation) surgery group.

(a) MSSM's February 28, 2001 report stated the following:

> "The informed consent document stated that '[I]f the study demonstrates that fetal nigral transplantation is safe and efficacious, nigral grafting will be offered to patients who have received a placebo operation. This is estimated to be in approximately 1999.' **This statement was, when written, a reasonable estimate of the likely timing of completion of participation and evaluation of the Study's success.** (emphasis added) Use of the words 'estimated' and 'approximately' was intended to convey the investigator's inability to place and exact date on the Study's conclusion and potential availability of grafts. Indeed, whether the Study would demonstrate that fetal nigral transplantation was safe and efficacious was uncertain, and could only be assessed after conclusion of the Study."

(b) The informed consent documents for the above-referenced research project [MSSM IRB approval dated from September 1, 1997 to August 31, 1999] stated the

following:

(i) "After 2 years we will compare the results in patients who received a fetal transplant with those who received a placebo operation without transplantation to see if fetal transplant helps the features of Parkinson's Disease."
(ii) "However, if you are randomized to the placebo group surgery group and the results of the study show significant benefit, you will be offered a transplant procedure in the final year of the study. This is estimated to be in the year 1999."

(iii) "If the study demonstrates that fetal nigral transplantation is safe and efficacious, nigral grafting will be offered to patients who have received a placebo operation. This is estimated to be in approximately 1999."

(c) The research participant list for the above-referenced study shows that eleven subjects were enrolled between March 3, 1998 and July 6, 1999.

Based on this information, OHRP finds that for the subjects described in (c) above, the MSSM IRB-approved informed consent document failed to accurately describe the timing of cross over to active intervention for subjects initially assigned to a placebo surgery group because the projected study completion dates for these subjects would have been after 1999.

Corrective Action: OHRP acknowledges MSSM's report stating that Dr. Olanow sent a letter to all enrolled subjects that stated the following:

"As the first months of year 2000 pass, I want to update you on the status of the Fetal Transplant program in Parkinson's disease. As you know, all patients have been enrolled in the program, and we are continuing to follow the last patients until they complete their two year evaluation. The last patient will finish the program in October 2001. At that time, we will analyze the results and compare the progress of patients who received neurotransplantation compared to those who did not. In the event that the transplantation procedure proves more effective than no surgical intervention, we will offer the better of the two transplant procedures to the patients in the placebo-treated group."

OHRP finds that this corrective action adequately addressed the above finding and is appropriate under the MSSM MPA.

As a result of the above determinations, 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 these determinations.

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

Sincerely,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Ruth Abramson, IRB Chair, MSSM
Dr. C.W. Olanow, MSSM
Dr. John Mather, Director, Office of Research Compliance and Assurance, Veterans Health Administration
Commissioner, FDA
Dr. David A. Lepay, FDA
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
Mr. George Gasparis, OHRP
Ms. Yvonne Higgins, OHRP
Mr. Barry Bowman, OHRP