DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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January 2, 2008

Dennis S. Charney, M.D.
Mount Sinai School of Medicine
1 Gustave L. Levy Place Box 1217, Attn: IRB Action
Annenberg Building, Room 2186
New York, NEW YORK 10029

RE: Human Research Subject Protections Under Federalwide Assurance FWA- 5656

Research Project: Immunological Basis of Egg Allergy
Principal Investigator: Dr. Anna Nowak Wegrzyn
Project Number: GCO #03-0609
Sponsor/ Funding Source: NIH 5K23AI059318-02

Research Project: Food Allergy Resource Initiative: Oral Food Challenge
Principal Investigator: Dr. Hugh Sampson
Project Number: GCO #04-0279
Sponsor/ Funding Source: Food Allergy Initiative (nonprofit foundation)

Research Project: The Natural History of Food Protein-Induced Enterocolitis Syndrome
Principal Investigator: Dr. Anna Nowak Wegrzyn
Project Number: GCO #03-0096
Sponsor/ Funding Source: Mount Sinai School of Medicine (MSSM) (unfunded)

Research Project: Food Allergen Genome Project
Principal Investigator: Dr. Hugh Sampson
Project Number: GCO #99-0538-B
Sponsor/ Funding Source: Food Allergy Initiative (nonprofit foundation)

Research Project: Immunologic Basis of Cow Milk-Induced Hypersensitivities
Principal Investigator: Dr. Hugh Sampson
Project Number: GCO #98-156
Sponsor/ Funding Source: NIH NIAID 5PO1AI044236-08

Research Project: Natural History of Milk Hypersensitivity and Diet Containing

Milk
Principal Investigator: Dr. Hugh Sampson
Project Number: GCO #01-1209
Sponsor/ Funding Source: MSSM (unfunded)

Research Project: Mechanism of Food Hypersensitivity in Atopic Dermatitis
Principal Investigator: Dr. Hugh Sampson
Project Number: GCO # 97-573
Sponsor/ Funding Source: MSSM (unfunded)

Research Project: Natural History of Peanut and Nut Protein Allergy
Principal Investigator: Dr. Hugh Sampson
Project Number: GCO #99-127
Sponsor/ Funding Source: MSSM (unfunded)

Research Project: Immunobiology of Peanut Allergy and Its Treatment: A Prototype
Principal Investigator: Dr. Scott Sicherer
Project Number: GCO #04-1271
Sponsor/ Funding Source: NIH 5U19AI066738-02

Dear Dr. Charney:

The Office for Human Research Protections (OHRP) has reviewed the Mount Sinai School of Medicine (MSSM) January 8, 2007 response to OHRP's November 29, 2006 letter of inquiry regarding allegations of possible noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above referenced research.

Based upon its review, OHRP makes the following determinations:

(1) It was alleged that a child with severe eczema was permitted to participate in a food challenge to beans even though the research protocol clearly stated that severe eczema is a contraindication for participation. OHRP acknowledges that MSSM audited all subjects in the protocols in question who received bean challenges for enrollment eligibility, that the protocols in which these patients were enrolled had no exclusion criteria for severe eczema, and that these subjects otherwise met entry criteria. OHRP therefore could not substantiate this allegation.

(2) It was alleged that there had been many anaphylactic reactions that necessitated the emergency administration of epinephrine and Solumedrol to treat life-threatening emergencies, but that the informed consent documents (ICD) merely state "there is a very small possibility of a severe allergic reaction (anaphylaxis) that could result in death, but this has never been reported during physician supervised food challenges."

OHRP acknowledges that the statement that, "there is a very small possibility of a severe allergic reaction (anaphylaxis) that could result in death, but his has never been reported during physician supervised food challenges," is accurate based on generally available data and experience at MSSM. OHRP also acknowledges that MSSM could not find any evidence that "life-threatening emergencies" had occurred in association with these studies. Therefore, OHRP is not able to substantiate the allegation that there had been "many anaphylactic reactions that necessitated the emergency administration of epinephrine and Solumedrol to treat life-threatening emergencies."

(3) OHRP notes that the ICD for studies GCO# 01-1209 and 03-0609 stated, "In case of a severe shock, you/your child will be given a shot of epinephrine (adrenaline)." This ICD language did not reflect the actual practice of the research investigators to give parenteral epinephrine at a much earlier stage for allergic reactions that were considerably milder than severe shock. OHRP therefore finds that the IRB-approved ICD for studies GCO# 01-1209 and 03-0609 failed to adequately address a description of the procedures to be followed in the research, as required by HHS regulations at 45 CFR 46.116(a)(2).

Corrective Actions: OHRP notes that studies GCO# 01-1209 and 03-0609 were suspended to new enrollment until ICDs for these studies were updated to reflect the practice of the research care providers to administer parenteral epinephrine at the earlier stages of an allergic reaction with the goal of preventing its progression to more serious forms. OHRP also acknowledges that the MSSM IRB reviewed and approved the new ICDs as well as communications to already enrolled subjects in studies GCO# 01-1209 and 03-0609 explaining the discrepancy and that those patients continuing in these studies will receive the revised information using the revised ICD.

OHRP finds that these corrective actions adequately address this finding and are appropriate under the MSSM FWA.

OHRP has the following guidance:

(4) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk, but not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. The IRB and investigators must plan ahead to meet required continuing review dates. If an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interest of currently enrolled subjects to continue participating in the research interventions or interactions. The IRB may consider a request for continued participation of all subjects currently enrolled. Enrollment of new subjects cannot occur after the expiration of IRB approval.

OHRP notes that the MSSM IRB Guidelines and Policies Manual (Revised March 2002, page 89) Section XV-Important Reminders to Investigators; subsection 1-IRB Submissions, states, "(1) If you have submitted your project for **renewal** and it is in the IRB review process, but is not approved prior to its termination date, you can **not** enroll additional subjects until the project receives final approval from the IRB." This is true only after a determination is made that continuing the research is in the best interest of already enrolled subjects. MSSM may wish to clarify this in the Guidelines and Policies Manual.

As a result, 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.

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,

Paul J. Andreason, MD
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:
Ms. Carol A. Bienstock, Administrative Director, MSSM
Dr. Jeff H. Silverstein, Chairperson, IRB/Assoc.Dean for Research, MSSM
Dr. Hugh Sampson, MSSM
Dr. Anna Nowak Wegrzyn, MSSM
Commissioner, FDA
Dr. Sherry Mills, Office of Extramural Research, NIH
Mr. Joseph Ellis, Office of Extramural Research, NIH
Dr. Ivor Pritchard, OHRP
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