DEPARTMENT OF HEALTH & HUMAN SERVICES

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November 3, 2000

Michael M. Gottesman, M.D.
Deputy Director for Intramural Research
National Institutes of Health
Building 1, Room 114
Bethesda, MD 20892

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1000

Research Project: Population Differences in the Insulin Sensitivity, Resting Energy Expenditure, and Body Composition of Overweight Children and Children of Overweight Parents
Protocol Number: 96-CH-0101
Principal Investigator: Jack A. Yanovski, M.D., Ph.D.

Dear Dr. Gottesman:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your December 21, 1998 report, as well as the current protocol and informed consent documents approved by the Institutional Review Board (IRB) and the most recent continuing review report, regarding the above referenced research. OHRP apologizes for the delay in responding to your report.

In reviewing the documents submitted to OHRP by the National Institutes of Health (NIH), OHRP notes the following regarding the above referenced research protocol:

(1) The initial research protocol approved by the National Institute of Child Health and Human Development (NICHD) IRB in April 1996 proposed to enroll 100 subjects from each of the following two populations:

(a) Obese, normal volunteers, age 6-10 years at the time of enrollment.

(b) Non-obese, healthy children of obese parents, age 6-10 years at the time of enrollment.

(2) The initial IRB-approved protocol includes the following interactions and interventions with the subjects at the time of enrollment and at five year intervals until the children reach adulthood:

(a) Medical history, measurement of vital signs, limited physical exam with Turner pubertal staging, and standardized psychological testing designed to uncover significant psychiatric illness.

(b) Fasting blood tests for normal metabolic, hepatic, renal, hematologic, and thyroid functions; leptin, IGF-I, IGF-II, GHBP, and IGFBP3 levels; genomic DNA isolation for beta-3 adrenergic receptor mutation determination; and estradiol, testosterone, DHEA-S, and androstenedione levels.

(c) Anthropometric assessment, including measurement of skinfold thickness, total body fat using bioeletrical impedance, and body circumference.

(d) Bone age X-ray.

(e) Screening two-hour oral glucose tolerance test.

(f) Twenty-four hour urine collection to measure urine free cortisol and creatinine.

(g) A two-day, one-night admission to the pediatric ward at the Clinical Center for the additional intensive testing described below.

(h) Leptin level diurnal rhythm study which involves placement of an intravenous (IV) line for 18 hours.

(i) Measurement of resting metabolic rate by indirect calorimetry using a respiratory metabolic cart.

(j) DEXA scanning for determination of lean body mass.

(k) MRI of the abdomen (without sedation) to determine visceral fat distribution.

(l) Two-hour hyperglycemic clamp study which involves placement of a second IV line, infusion of glucose intravenously for two hours (to maintain blood sugar at 180 mg/dl), and blood sampling at five-minute intervals for measurement of glucose, free fatty acids, and insulin.

(m) Three-hour euglycemic, hyperinsulinemic clamp study which involves two IV lines, infusion of glucose and insulin intravenously for three hours (to maintain

blood sugar at 80 mg/dl), and blood sampling at five-minute intervals for measurement of glucose, free fatty acids, and insulin.

(n) Pregnancy testing for all post-menarchal girls.

(o) Prior to blood draws and IV line placements, EMLA cream is applied to the subjects' skin.

(3) The minutes for the March 27, 1996 NICHD IRB meeting include the following statements:

(a) "Because euglycemic and hyperglycemic clamp techniques involve several hours of intravenous infusions, the Committee agreed that the level of risk to which children enrolled in this study will be exposed falls within Section 46.406 of 45 CFR 46, Subpart D, namely, research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Furthermore, the planned procedures will present experiences to the subjects that are reasonably commensurate with those inherent in their actual or expected medical condition."

(b) "Committee Recommendation: The Committee voted unanimously to approve this protocol with the stipulations noted above."

(4) The minutes of the April 24, 1996 NICHD IRB meeting include the following statements:

(a) "Dr. Yanovski appeared before the Committee to explain the risk involved in euglycemic and hyperglycemic clamp experiments. He emphasized that the risk is minimal. He noted that no episodes of hypoglycemia have been experienced by any of the hundreds of children who have participated in this kind of clamp experiment at [another institution]. . . ."

(b) "A physician will be in constant attendance during the procedure, and blood sugar will be tested every five minutes during the clamp."

(c) "Several members of the Committee explored the meaning of minimal risk and what a child might encounter in a visit to the doctor or while playing in traffic. It was felt that spending several hours in the Clinical Center in a clamp experiment would be safer than playing actively on sidewalks and streets. Certainly, visits to the orthodontist, which may entail removal of multiple teeth, are not risk-free. It was also noted that performing multiple procedures each with low risk adds up to an integral summation of risk that may exceed minimal risk. Even if the procedures are staggered, this integrated risk is the same. Other members of the

Committee felt that for this protocol such an integral would still remain at the level of minimal risk since each procedure entails only minimal risk."

(d) "One member of the Committee noted that normal children are given o-CRH tests and GH stimulation tests that involve equivalent or greater risk than the clamp experiments proposed by Dr. Yanovski."

(e) "Committee Recommendation: The Committee agreed unanimously that the level of risk to which children enrolled in this protocol are exposed falls within Section 46.404 of 45 CFR 46, Subpart D, namely not greater than minimal risk, and stipulated that Dr. Yanovski describe the clamp procedure in the protocol in greater detail."

(5) Since the time of initial approval in April 1996, the following modifications to the protocol have been approved by the IRB:

(a) The target blood glucose for the euglycemic, hyperinsulinemic and the hyperglycemic clamp procedures were increased to 100 mg/dl and 200 mg/dl, respectively (September 1996).

(b) The duration of the leptin level diurnal variation study was increased to 21 hours (September 1996).

(c) Measurement of total daily energy expenditure by using the doubly labeled water technique was added to the intensive evaluation done at baseline and at five year intervals (November 1996). This procedure required a daytime admission to the Clinical Center on two different days over a one-week time period.

(d) The two clamp procedures were temporally separated so that the euglycemic, hyperinsulinemic clamp procedure was performed during a second separate day-time admission to the Clinical Center (February 1997).

(e) A pelvic ultrasound procedure was added to the to the intensive evaluation done at baseline and at five year intervals for girls (February 1997).

(f) Yearly health evaluations with nutrition assessment, medical history, physical exam, and psychological questionnaires were added for all subjects (August 1997).

(g) One-week monitoring for heart rate and physical activity was added to the intensive evaluation done at baseline and at five year intervals (August 1997). This procedure required having the subjects wear a wrist band and chest belt monitor system.

(h) The euglycemic, hyperinsulinemic clamp procedure was discontinued (February 1999).

(i) Body fat measurement via air displacement plethysmography, lean body mass and body fat mass measurement by DEXA scan (only at years 1 and 3), bioeletric impedance, and bone age x-rays (only at years 1 and 3) were added to the yearly follow-up visits (February 1999).

(j) Target enrollment of normal weight children was increased to 150 (June 2000).

(6) As of October 2000, 100 obese children and 93 normal weight children had been enrolled in this research project.

OHRP Findings

Based upon its review, and after consultation with outside experts who have expertise in the areas of bioethics, pediatrics, radiology, biomedical research, and human subject protections, OHRP makes the following determinations regarding the above referenced research:

(1) HHS regulations at 45 CFR 46.102(i) define minimal risk as the level of risk for which the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

OHRP acknowledges that determinations regarding the risk level of research are based upon the subjective judgement of the IRB. Nevertheless, after taking into account the level of risk assigned to research similar to protocol #96-CH-0101 by other like institutions, OHRP finds that this research involves greater than minimal risk. In particular, the hyperglycemic and euglycemic, hyperinsulinemic clamp procedures involve greater than minimal risk. Other study interventions, such as the two-day, one-night hospitalization for intensive metabolic evaluation, the MRI procedure, and the leptin level diurnal rhythm study, may also involve greater than minimal risk for some subjects. Therefore, the research does not represent the category of research involving children permissible under HHS regulations at 45 CFR 46.404.

(2) OHRP finds that the research does not present the prospect of direct benefit to any of the subjects. Therefore, the research does not represent the category of research involving children permissible under HHS regulations at 45 CFR 46.405.

(3) Regarding the non-obese healthy children, OHRP finds that these subjects do not have a disorder or condition. Furthermore, for both the non-obese healthy children and the obese healthy children, many of the interventions and procedures do not present experiences to the subjects that are reasonably commensurate with those inherent in their

actual or expected medical, dental, psychological, social, or educational situations, and some of the interventions may involve a level of risk that exceeds a minor increase over minimal risk. Therefore, the research does not represent the category of research involving children permissible under HHS regulations at 45 CFR 46.406.

(4) OHRP finds that this research may only be conducted by HHS if the requirements of HHS regulations at 45 CFR 46.407 are satisfied. In particular, OHRP, acting on behalf of the Secretary of HHS, would need to consult with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, and law), provide an opportunity for public review and comment, and make the determinations required under HHS regulations at 45 CFR 46.407(b)(1) prior to the initiation of the research. OHRP finds that these requirements have not been satisfied for this research.

Required Actions:

In view of the above determinations and in order to ensure adequate protection of human subjects, OHRP requires that NIH take the following actions:

Action 1: NIH must suspend immediately the above referenced research project. Under this suspension, no new subjects may be enrolled in the research and research interventions and interactions in currently enrolled subjects must cease. This suspension must remain in effect until either (a) the research is modified in a manner that would satisfy the criteria for one of the permissible categories of research under HHS regulations at 45 CFR 46.404-406, and the IRB re-reviews the research and makes and documents the required findings; or (ii) the requirements of HHS regulations at 45 CFR 46.407 are fulfilled by OHRP, acting on behalf of the Secretary of HHS.

Please note that OHRP is prepared to assist NIH in satisfying the requirements of HHS regulations at 45 CFR 46.407 in an expeditious manner. In particular, OHRP has begun to identify individuals who could serve on the required panel of experts in the near future.

Action 2: The NICHD IRB must review the above findings and determine an appropriate course of action. In particular, the IRB should consider whether it would be appropriate to develop a plan, including both the means and the content, for contacting the parents or guardians of the subjects who participated in the above referenced research and informing them of their children's inappropriate enrollment in this research. By December 8, 2000, please submit to OHRP a written report regarding the IRB's determinations in this matter and the documentation underlying these determinations, including relevant IRB minutes and any proposed text for debriefing the parents or guardians of the subjects.

Action 3: By December 8, 2000, NIH must submit to OHRP a satisfactory corrective action plan to address the above findings and prevent such noncompliance from recurring.

Action 4: By December 8, 2000, NIH must provide OHRP with a list of all active research protocols being conducted by the NIH intramural research program that involves normal, healthy children. Please include the following information with this list: project title, principal investigator name, IRB protocol number, the supporting NIH institute, a description of the research that includes a summary of all research interactions and interventions and the age range of the subjects, and documentation of the IRB's determinations under HHS regulations at 45 CFR 46.404-46.407.

Additional OHRP Questions and Concerns

OHRP has the following additional questions and concerns regarding the above referenced research:

(1) The research protocol initially approved by the IRB stated the following on page 20:

> "Previous NICHD protocols have allowed investigators to perform insulin tolerance tests designed to induce hypoglycemia (a blood sugar <50 mg/dL) in normal children."

Please provide OHRP with the complete IRB file for any protocols that included such an insulin tolerance test in normal children. Please include the following for each such protocol:

(a) The IRB-approved research protocol.

(b) The IRB-approved informed consent and assent documents.

(c) The relevant IRB minutes, including initial review, continuing review, review of changes to the research or the informed consent documents, and review of any adverse or unanticipated problems.

(d) All correspondence between the IRB and the investigators.

(e) All continuing review reports.

(f) A list of subjects (code number only) with date of enrollment and subject age.

(g) A chronological summary of the dates of the IRB's actions.

(h) A copy of any publications, abstracts, or presentations which were derived from the research.

(i) Any other pertinent information.

(2) When the IRB reviewed and approved the initial research protocol on March 27, 2000, the IRB initially found the research to represent the category of research involving children permissible under HHS regulations at 45 CFR 46.406. It appears that at that time the IRB failed to make and document the finding required by HHS regulations at 45 CFR 46.406(c)(i.e., the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition). Please respond.

(3) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP is concerned that the informed consent document approved by the IRB for this study includes complex language that would not be understandable to the parents or guardians of all subjects. Please respond.

(4) OHRP is concerned that the informed consent documents reviewed and approved by the IRB for this research protocol failed to include an adequate description of the reasonably foreseeable risks and discomforts of the research, as required by HHS regulations at 45 CFR 46.116(a)(2). In specific, it appears that it would have been appropriate to describe the following reasonably foreseeable risks associated with the research:

(a) The risk of thrombophlebitis from the IV lines.

(b) The risks associated with EMLA cream, such as local irritation and allergic or anaphylactoid reactions.

(c) Risks of incidental abnormalities or false positive results that may occur during the large number of screening and diagnostic tests and may result in further unnecessary medical evaluations and anxiety.

(d) The risk of medication errors that can occur during hospitalization (e.g., errors in insulin dosing).

Please respond.

(5) It appears that it would have been appropriate for the informed consent documents to include the following additional elements in accordance with HHS regulations at 45 CFR 46.116(b):

(a) Section 46.116(b)(2): The anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(b) Section 46.116(b)(4): The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(c) Section 46.116(b)(5): A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

Please respond.

Please submit your response to the above referenced concerns and questions by December 8, 2000.

OHRP appreciates the commitment of your institution to the protection of human subjects.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. Ruth Kirschstein, Acting Director, NIH
Dr. Duane Alexander, Director, NICHD
Dr. Alan Sandler, Director, OHSR, NIH
Dr. Gilman Grave, Chair, IRB, NICHD, NIH
Dr. Jack Yanovski, NICHD, NIH
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