DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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1101 Wootton Parkway, Suite 200
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May 27, 2003

TO: Surgeon General and Acting Assistant Secretary for Health

FROM: Acting Director, Office for Human Research Protections

SUBJECT: HHS Support For Research–ACTION

ISSUE

Recommendation by the Office for Human Research Protections (OHRP) that the Department of Health and Human Services (HHS) support the proposed research protocol entitled "Precursors to Diabetes in Japanese American Youth," subject to specific stipulations outlined below. In making this recommendation, OHRP has considered the opinions of experts as well as comments received from the public, in accordance with 45 CFR 46.407. The proposed research is not otherwise approvable under subpart D of 45 CFR part 46.

DISCUSSION

All studies conducted or supported by HHS that are not otherwise exempt and that propose to involve children as research subjects require institutional review board (IRB) review in accordance with the provisions of HHS regulations at 45 CFR part 46, subpart D. Pursuant to HHS regulations at 45 CFR 46.407, if an IRB reviewing a protocol to be conducted or supported by HHS does not believe that the proposed research involving children as subjects meets the requirements of HHS regulations at 45 CFR 46.404 (research not involving greater than minimal risk), 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects), or 46.406 (research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition), but was suitable for review under the procedure provided in 45 CFR 46.407 (research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children), the research may proceed only if the following conditions are met: (a) the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and (b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406, or (2) that the following conditions are met: (i) the research presents a

reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) the research will be conducted in accordance with sound ethical principles; and (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

In 2001, a research proposal entitled "Precursors to Diabetes in Japanese American Youth" was submitted to OHRP by the University of Washington on behalf of the principal investigator, Dr. Wilfred Y. Fujimoto. The institution's designated IRB determined that the research protocol presented more than minimal risk to participants and did not provide the prospect of direct benefit to the individual subjects and therefore could not approve the research under 45 CFR 46.404 or 45 CFR 46.405, respectively. While the IRB found that the risks to subjects represented a minor increase over minimal risk, the research participants did not have a disorder or condition; therefore, the IRB could not approve the research under 45 CFR 46.406. The IRB determined, however, that the research presented a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children and was suitable for review under 45 CFR 46.407.

The proposed research would be supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (1 R01 DK59234-01). The long-term aim of the proposed study is to increase understanding about the metabolic changes that precede the development of type 2 diabetes in children and the influence of Asian ethnicity on the risk of developing type 2 diabetes.

The first hypothesis to be tested is that features of the insulin resistance metabolic syndrome (abnormal response to insulin, high blood pressure, and abnormalities of blood cholesterol and other lipids) will be found in some prepubertal children. The metabolic and obesity-related factors associated with the insulin resistance syndrome will be determined. These factors include fasting plasma lipids (cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol), LDL size, blood clotting factors (plasminogen activator inhibitor-1, fibrinogen, C-reactive protein), glucose, insulin, C-peptide, and proinsulin; glucose tolerance; total body fat; body fat distribution; intra-abdominal fat measured by Magnetic Resonance Imaging (MRI); and body mass index.

The ability of the beta cells of the pancreas to make and secrete insulin will be assessed to test the hypothesis that pancreatic beta-cell dysfunction will be evident in some children. Measurements of fasting plasma insulin, C-peptide, proinsulin and the acute insulin response to glucose during an intravenous glucose tolerance test (IVGTT) will be obtained.

The next hypothesis to be tested states that puberty is associated with changes in body fat distribution and metabolic parameters which could lead to higher risk of glucose intolerance and cardiovascular disease. Diet and physical activity, which are important predictors of body fat level and metabolism, will be assessed.

Finally, metabolic and obesity-related factors will be determined to test the hypothesis that a higher proportion of children with Japanese ancestry will have a greater predisposition to the metabolic syndrome and diminished insulin secretion. In addition, collection of DNA is proposed for future genetic studies. (For more details, see Tab A- Clinical Trial Outline).

In August 2001, OHRP assembled a panel of experts in accordance with the provisions of HHS regulations at 45 CFR 46.407. The majority of the experts on the panel, as individually expressed, found that the protocol presented a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children, and could be approved appropriately under 45 CFR 46.407, contingent upon modifications to the protocol to further minimize the risks to the participants, as well as modifications to the assent and parental permission documents. (See Tab B - OHRP Report on Expert Panel Review, prepared in June 17, 2002.) The recommended modifications included (1) ensuring appropriate pediatric expertise in conducting the IVGTT; (2) minimizing the risks from DNA banking by taking steps to ensure the confidentiality of the subjects; and (3) including clear exclusion criteria for MRI studies.

On August 7, 2002, a *Federal Register* Notice was published regarding OHRP's intent to recommend HHS support for this research protocol contingent upon specific modifications, and public review and comment were solicited for a period of 14 days. During this period, OHRP received a total of ten comments; eight of these expressed strong concerns that the length of time and the materials made available for public review were insufficient to provide meaningful comment. Based on the information provided, eight of the ten comments objected to HHS funding of this research. Several of the comments questioned the scientific validity of the research; three comments questioned the adequacy of the methodology to evaluate the possible relationship between Japanese ancestry and type 2 diabetes. (See Tab C for a tabular summary of public comments.)

On December 18, 2002, a *Federal Register* Notice was published reopening public comment for a period of 30 days and providing additional materials for review including: (1) relevant excerpts of the grant application; (2) the IRB-reviewed protocol application; (3) consent form; (4) assent form; and (5) OHRP Report on Expert Panel Review. A total of three comments were received during this period. (See Tab C.) Two of these comments were received from individuals who had submitted comments following the first public review period. Upon review of the additional documents related to the protocol, these two commenters remained opposed to the conduct of the study because of continued concerns regarding the scientific validity of the study.

OHRP has reviewed the research protocol and considered the recommendations provided by the experts and the comments received from the public. Contingent upon specific modifications to the proposed research protocol as outlined below, OHRP finds that the research may be approved under 45 CFR 46.407, and recommends that HHS support the proposed research protocol.

The required modifications are as follows:

(1) The IVGTT must be performed in a location with adequate pediatric expertise which would include pediatricians, pediatric nursing, and phlebotomists who are trained and experienced in handling pediatric patients.

(2) The risks from the DNA banking must be minimized by:

- (a) Outlining specific procedures in the protocol for protecting the privacy and confidentiality of the subjects with respect to genetic testing, including physical security of stored samples, whether the samples will be labeled with code numbers or stripped of identifiers that can be linked to the subject, and how genetic information will be kept separate from the subject's medical record;
- (b) Re-consenting the subjects when they reach the age of maturity specified by the State of Washington;
- (c) Providing information within the assent and permission documents about whom to call if the subject or parent wishes to have DNA samples removed from the bank and destroyed or have all personal identifiers be removed;
- (d) Providing within the assent and permission documents a description of the potential psychological, legal, and social risks of genetic research; and
- (e) Including a statement within the assent and permission documents regarding subjects' or parents' access to information learned from the research, if they so choose. The statement should include the investigator's policy regarding disclosure of interim results and/or incidental findings gained from the banked DNA samples.

(3) The protocol must include clear exclusion criteria for MRI studies, including claustrophobia and the need for procedural sedation, with these exclusion criteria explained in the parental permission document and the subject's assent form.

(4) The research protocol must be revised to:

- (a) Describe more precisely and in greater detail how racial and/or ethnic groups will be defined;
- (b) Provide a more specific definition of the insulin resistance metabolic syndrome and relate this case definition to the long term aim of the study, e.g., to understand the metabolic changes that precede the development of type 2 diabetes;
- (c) Describe methods used to adjust for confounding or chance in the differences observed among study groups; and
- (d) Outline the methods for minimizing bias in the recruitment of different study groups.

Once these stipulations have been incorporated into the research protocol, permission/assent forms, and other documents as appropriate, and these changes have been approved by the reviewing IRB and confirmed by OHRP, the proposed research would be in conformance with 45 CFR 46, subpart A, and 45 CFR 46, subpart D, sections 46.407 and 46.408 and may be supported by HHS.

In addition to requiring that the proposed research protocol be modified as stipulated above, OHRP will provide the following guidance to the investigators and the reviewing IRB:

(1) Additional OHRP guidance on tissue bank repositories can be found on the OHRP website at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm.

(2) Where appropriate, an IRB may find that the informed consent document/process for research involving obtaining DNA samples for genetic testing should include some or all of the following types of information:

(a) A statement that the samples will be sent to researchers at other institutions for genetic testing and the conditions under which samples will be sent (i.e., with or without subject identifiers);
(b) A statement regarding the length of time that samples will be stored. If storage time is indefinite, so state;
(c) A statement regarding secondary uses of the DNA samples. For example, state that (i) there will be no secondary use, or (ii) subjects have the option of allowing secondary use of banked DNA samples, or (iii) subjects will be contacted for additional consent in the future if the researchers wish to make secondary use of the banked samples, or (iv) there will be secondary use only after the banked samples have been stripped of identifiers; and
(d) A statement regarding third-party (family members, physicians, employers, insurance companies) access to the DNA samples and data.

OHRP bases its recommendation on the reports of experts who have reviewed this research protocol, comments received during the public review and comment period, and its own analysis of the proposed research protocol. OHRP finds that the research is not approvable under 45 CFR 46.404 because the research involves procedures such as the IVGTT that constitute greater than minimal risk to the subjects. OHRP finds that the research may not be approved under 45 CFR 46.405 because the proposed protocol involves healthy children who are unlikely to directly benefit from participation in this research. Because the subjects to be enrolled in this study are healthy children who do not have a disorder or condition, OHRP finds that this research may not be approved under 45 CFR 46.406.

OHRP has determined that the research protocol reaches the threshold required for approval under the provisions set forth in 45 CFR 46.407, provided that the modifications specified above have been satisfactorily integrated into the research protocol. The proposed research, if so modified, would (i) present a reasonable opportunity to further the understanding, prevention, or alleviation of type 2 diabetes in children, which is a serious problem affecting the health or welfare of children; (ii) be conducted in accordance with sound ethical principles; and (iii) have adequate provisions for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

In determining that the research would be conducted in accordance with sound ethical principles, OHRP has considered that the research, if modified as outlined above, would meet the relevant requirements set forth in 45 CFR 46, subpart A, including 45 CFR 46.111(a)(2) which requires that the risks to subjects are reasonable in relation to the importance of the knowledge that may reasonably be expected to result. If requested modifications are satisfactorily incorporated, OHRP considers that the proposed research protocol would present a minor increase over minimal risk and believes that the knowledge to be gained by this study would provide an important foundation for subsequent studies investigating the risk factors associated with the development of type 2 diabetes in children and the potential influence of Japanese ancestry on diabetes risk. The research would also fulfill the provisions of 45 CFR 46.111(a)(3) which requires that the selection of research subjects be equitable and that the research setting be particularly cognizant of the special problems of research involving children. The use of children as subjects in the proposed research is scientifically justified because the central objectives of the research, i.e., to describe the metabolic and obesity-related factors associated with the insulin-resistance metabolic syndrome in prepubertal and pubertal children, and to evaluate how diet, exercise, and pubertal changes in metabolic and adipose factors affect diabetes risk in Japanese and Caucasian children, could not be effectively investigated in populations other than the population proposed.

The majority of experts (six of seven) assembled to evaluate this research protocol recommended that HHS support the proposed research under 45 CFR 46.407, contingent upon specific modifications to further minimize the risks to children. These consultants included nationally recognized experts in pediatric endocrinology, diabetes, and biomedical ethics. The one expert who did not recommend approval of this research felt that the study contained serious design flaws. She argued that the sample size was inadequate because only 42 percent of children would reach puberty during the study period and only one subject would develop diabetes, based on the statistical projections of the investigators, and that this proposal would yield little reliable information to help better understand, prevent, or alleviate type 2 diabetes in children.

OHRP is recommending that HHS support this research despite one expert's reservations and the fact that the majority of public comments opposed the conduct of this research because: (1) OHRP is requiring additional modifications to the research protocol, as outlined above, to provide further protections for research participants and to address concerns regarding the study's

scientific validity and methodology; (2) several public comments objecting to HHS support of the study were made prior to the public availability of additional documents relating to the research during the second review period, and it is OHRP's assessment that many of those objections were adequately addressed through release of the additional documents; (3) the primary aims of this study are descriptive in nature and the sample size appears adequate to meet the stated objectives; and (4) the results of this study will likely be helpful in identifying questions to be addressed by subsequent studies investigating the relationship between metabolic and adipose factors, diet, exercise, and ethnicity on the development of type 2 diabetes, which constitutes a serious problem affecting the health and welfare of children.

RECOMMENDATION

I recommend HHS support of this research protocol, contingent upon revision of the protocol, permission/assent forms, and other documents as appropriate, in accordance with the required modifications outlined above. These modifications must be approved by the reviewing IRB and confirmed by OHRP, prior to the involvement of human subjects. If the protocol is modified accordingly, the criteria of 45 CFR 46.407 and 45 CFR 46.408 will be met.

DECISION

/s/ Cristina V. Beato, M.D./ for
Approved Richard Carmona Disapproved _____ Date [6/5/2003]

/s/ Bernard A. Schwetz

Bernard A. Schwetz, D.V.M., Ph.D.

3 Attachments:
Tab A - Clinical Trial Outline
Tab B - Report of Expert Panel Review Prepared June 17, 2002
Tab C -Tabular Summary of Public Comments