DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 301-496-7005
FAX: 301-402-2071

July 11, 2003

Douglas S. Diekema, M.D., M.P.H.
Chairman, Institutional Review Board
Children's Hospital and Regional Medical Center
Research Administration 7G-3
4800 Sand Point Way NE
PO Box 5371
Seattle, WA 98105-0371

Subject: **Secretary's Determination under Department of Health and Human Services Regulations at 45 CFR 46.407 on the Research Protocol Entitled "Precursors to Diabetes in Japanese-American Youth" (1 R01 DK59234-01); Principal Investigator Dr. Edward Boyko**

Dear Dr. Diekema:

This letter is written on behalf of the Assistant Secretary for Health (ASH), Department of Health and Human Services (HHS). In 2001, Children's Hospital and Regional Medical Center (CHRMC) institutional review board (IRB) forwarded the above-referenced protocol to the Office for Human Research Protections (OHRP) for consideration pursuant to requirements of the HHS regulations at 45 CFR 46.407 (i.e., research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children). The proposed research protocol would be funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH) under grant number 1 R01 DK59234-01.

In accordance with the requirements of 45 CFR 46.407, HHS solicited opinions regarding the proposed study from experts in relevant disciplines in August 2001. 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. Because several comments received during this period expressed concern that the length of time and the materials made available for public review were insufficient to provide meaningful comment, 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 on the OHRP website at http://ohrp.osophs.dhhs.gov/pdjay/pdjayindex.htm. These materials included: (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. The second and final public comment period ended on January 17, 2003.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 301-496-7005
FAX: 301-402-2071

July 11, 2003

Douglas S. Diekema, M.D., M.P.H.
Chairman, Institutional Review Board
Children's Hospital and Regional Medical Center
Reg. CHRMC Administration 7C-3
4800 Sand Point Way NE
PO Box 5371
Seattle, WA 98105-0371

Subject: Secretary's Determination under Department of Health and Human Services Regulations at 45 CFR 46.407 on the Research Protocol Entitled "Precursors to Diabetes in Japanese-American Youth" (1 R01 DK59234-01); Principal Investigator Dr. Edward Boyko

Dear Dr. Diekema:

This letter is written on behalf of the Assistant Secretary for Health (ASH), Department of Health and Human Services (HHS). In 2001, Children's Hospital and Regional Medical Center (CHRMC) institutional review board (IRB) forwarded the above-referenced protocol to the Office for Human Research Protections (OHRP) for consideration pursuant to requirements of the HHS regulations at 45 CFR 46.407 (i.e., research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children). The proposed research protocol would be funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH) under grant number 1 R01 DK59234-01.

In accordance with the requirements of 45 CFR 46.407, HHS solicited opinions regarding the proposed study from a panel of experts in relevant disciplines in August 2001. On August 7, 2002, a *Federal Register* Notice was published regarding OHRP's intent to recommend HHS support for this research protocol with specific modifications, and public review and comment were solicited for a period of 14 days. Because several comments received during this period expressed concern that the consent and assent materials made available for public review were insufficient to provide meaningful comment, on December 18, 2002, a *Federal Register* Notice was published announcing public comment for a period of 30 days and providing additional materials for review on the OHRP Web site at http://ohrp.osophs.dhhs.gov/pdjay/pdjayindex.htm. These materials included: (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. The second and final public comment period ended on January 17, 2003.

Following consideration of the research protocol, recommendations by the experts, and comments received from the public, the ASH found that the research may be approved under 45 CFR 46.407, and recommended that HHS support the proposed research protocol, contingent upon specific modifications to the proposed research protocol as outlined below. The proposed research protocol, so modified, would be in conformance with 45 CFR 46, subpart A; as well as 45 CFR 46, subpart D, sections 46.407 and 46.408 which require that the research (i) present a reasonable opportunity to further the understanding, prevention, or alleviation of 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. For your reference, the ASH's decision memorandum is enclosed with this correspondence.

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 for protecting the privacy and confidentiality of the subject, with respect to genetic testing, including physical security of stored samples, whether the samples will be labeled with a code number or name, 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 how 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 written specific modifications and public review and comment were solicited for a period of 14 days. Because several comments received during this period expressed concern that the consent and assent materials made available for public review were insufficient to provide meaningful comment, on December 18, 2002, a *Federal Register* Notice was published announcing public comment for a period of 30 days and providing additional materials for review on the OHRP Web site at http://ohrp.osophs.dhhs.gov/pdjay/pdjayindex.htm. These materials included: (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. The second and final public comment period ended on January 17, 2003.

Following consideration of the research protocol, recommendations by the experts, and comments received from the public, the ASH found that the research may be approved under 45 CFR 46.407, and recommended that HHS support the proposed research protocol, contingent upon specific modifications to the proposed research protocol as outlined below. The proposed research protocol, so modified, would be in conformance with 45 CFR 46, subpart A; as well as 45 CFR 46, subpart D, sections 46.407 and 46.408 which require that the research (i) present a reasonable opportunity to further the understanding, prevention, or alleviation of 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. For your reference, the ASH's decision memorandum is enclosed with this correspondence.

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 for protecting the privacy and confidentiality of the subject, with respect to genetic testing, including physical security of stored samples, whether the samples will be labeled with a code number or name, 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 how 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 written specific modifications and public review and comment were solicited for a period of 14 days. Because several comments received during this period expressed concern that the consent and assent materials made available for public review were insufficient to provide meaningful comment, on December 18, 2002, a *Federal Register* Notice was published announcing public comment for a period of 30 days and providing additional materials for review on the OHRP Web site at http://ohrp.osophs.dhhs.gov/pdjay/pdjayindex.htm. These materials included: (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. The second and final public comment period ended on January 17, 2003.

(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.

These stipulations must be incorporated into the research protocol, permission/assent forms, and other documents as appropriate, approved by the reviewing IRB, and confirmed by OHRP, prior to HHS funding of the research protocol and the enrollment of human subjects. Once the requested stipulations have been incorporated into the protocol and related documents and approved by the IRB, the IRB should then forward the approved protocol to OHRP. Upon confirmation that the requested changes have been made, OHRP will send a letter to the IRB and principal investigator indicating that enrollment may begin.

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

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

(6) 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.

Please do not hesitate to contact us with any questions. Thank you for your continuing commitment to the protection of human subjects.

Sincerely,

/s/ Bernard A. Schwetz

Bernard A. Schwetz, D.V.M.., Ph.D.
Acting Director
Office for Human Research Protections

Enclosures

cc: Dr. Edward Boyko, University of Washington
Dr. Richard Molten, CHRMC
Ms. Elisabeth Trias, CHRMC
Dr. Lana Skirboll, NIH
Dr. Belinda Seto, NIH
Dr. Allen M. Spiegel, NIDDK, NIH
Dr. Barbara Linder, NIDDK, NIH
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Irene Stith-Coleman, OHRP
Dr. Leslie Ball, OHRP
Ms. Patricia El-Hinnawy, OHRP