Report on Expert Panel Review Under Subpart D of 45 CFR 46

Precursors to Diabetes in Japanese American Youth
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Investigator: Dr. Wilfred Y. Fujimoto
University of Washington

Convened on August 13-14, 2001

EXECUTIVE SUMMARY

On May 23, 2001, the Office for Human Research Protections (OHRP) received a request from the University of Washington of Seattle, Washington to consult a panel of experts in accord with Title 45, Part 46, Section 407 of the Code of Federal Regulations. The purpose of the panel was to examine the inclusion of children as research subjects in an experimental protocol entitled "Precursors to Diabetes in Japanese American Youth".

The panel of experts convened on August 13 and 14, 2001. This report summarizes the experts' individual findings. The principal responsibilities of the experts were to determine either (a) that the research in fact satisfies the requirements of 45 CFR §46.404, §46.405, or §46.406, or (b) that (i) the research presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health and 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 and guardians.

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, contingent upon modifications to the protocol and consent forms to further minimize the risks to the participants. Once these recommended modifications have been implemented, the research would be conducted in accordance with sound ethical principles, and adequate provision would be made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408; and would be in conformance with the requirements of 45 CFR §46.407.

BACKGROUND

On May 23, 2001, the Office for Human Research Protections (OHRP) received a request from the Children's Hospital and Regional Medical Center of Seattle, Washington for the Department of Health and Human Services (HHS) to consult a panel of experts to examine the inclusion of children as research subjects in an experimental protocol proposed at that institution, entitled "Precursors to Diabetes in Japanese American Youth". The institution's designated Institutional Review Board (IRB) determined that the research could not be approved under 45 CFR §46.404, §46.405, or §46.406,

but is suitable for review under 45 CFR §46.407. Although the IRB found that the research was not designed to provide direct benefit to subjects, it found that the research presented a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children. The IRB considered the protocol to be important research and was favorably impressed with the scientific approach of the investigators.

As required under the regulations at 45 CFR §46.407, a panel of experts was convened on August 13 and 14, 2001 to individually advise the Secretary of HHS, through OHRP, on the acceptability of the protocol in regard to requirements of 45 CFR §46.407.

Applicable Regulations

HHS regulations for the protection of human research subjects, 45 CFR part 46, include specific provisions regarding the involvement of children as research subjects. Children may be involved in such research only after the responsible IRB has determined that the specific requirements detailed in Subpart D of 45 CFR part 46 have been met.

Research involving children that provides no direct, individual benefit to the subjects, that is not otherwise approvable under Subpart D of 45 CFR part 46, can only be approved pursuant to 45 CFR §46.407. Under §46.407, (1) the IRB must find that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children, and (2) the Secretary of HHS, after consultation with a panel of experts in pertinent disciplines and following opportunities for public review and comment, must determine either (a) that the research in fact satisfies the conditions of 45 CFR §46.404,
§46.405, or §46.406, or (b) that (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and 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 §46.408.

Scientific Background

Type 2 diabetes, characterized by insulin resistance, is the most common form of diabetes in adults. It was rarely diagnosed in children until about 10 years ago and since then there has been a dramatic, ten-fold increase. This increase in the prevalence of type 2 diabetes in children has been attributed to a simultaneous increase in the incidence of childhood obesity.

Asian adults, despite a low prevalence of obesity, have a predisposition to accumulate central, abdominal fat and have an increased risk for type 2 diabetes. While there are no data on the prevalence of type 2 diabetes in Asian-American children, recent studies of Japanese school children in Japan have demonstrated an increase in obesity as well as type 2 diabetes. It is predicted that Japanese-American children living in the United States would be affected by both obesity and type 2 diabetes to even a greater extent. However, the time of greatest risk for developing type 2 diabetes is around the time of puberty. Therefore, the proposed study will determine the influences of both ancestry and pubertal hormone effects on glucose metabolism and insulin resistance and the risk of

developing type 2 diabetes in children. The results of the studies should be relevant to other Asian populations living in the United States.

SUMMARY OF THE PROPOSED RESEARCH

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 diabetes risk.

In this longitudinal study, it is proposed that a cohort of 450 healthy children be enrolled who are 8 to 10 years of age. Three hundred children will be of Japanese ancestry, while the other 150 children will be their Caucasian cousins. Each subject will have two evaluations (two years apart, one at baseline and the other at the two year follow-up). At each evaluation, the subjects will undergo the following procedures: (i) medical and family history; (ii) physical activity and dietary assessment; (iii) physical examination including pubertal staging; (iv) blood drawn by venipunture to measure the level of multiple hormones, lipids, and other serum factors and proteins; (v) intravenous glucose tolerance test which involves placement of an intravenous catheter, infusion of glucose, and serial measurements of serum levels of glucose, and insulin, and other factors; and (vi) measurement of body composition by means of DEXA and intra-abdominal fat determination by MRI.

The first hypothesis to be tested is that features of the 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), 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 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 be associated with a greater predisposition to the metabolic syndrome and diminished insulin secretion. In addition, collection of DNA is proposed for future genetic studies.

EVALUATION BY PANEL OF EXPERTS

The panel of experts, as detailed in their individual findings, found that the risks to the subjects had been minimized and that subject recruitment was equitable, as required under 45 CFR §46.111. The experts further found that the study represented greater than minimal risk for children who would not have the prospect of direct, individual benefit and who did not have a disorder or condition at the time of the proposed study, and thus can only be funded by HHS if the requirements of §46.407 are met.

Degree of Risk

The panel of experts determined that certain proposed test procedures caused the risks of the proposed research to be classified as a minor increase over minimal risk. Discussion of proposed tests included intravenous glucose tolerance test (IVGTT), DNA banking for future tests, and Magnetic Resource Imaging (MRI).

To further minimize the risks to the participants, the experts made the following recommendations:

1. The IVGTT be performed in a pediatric location with adequate pediatric expertise which would include pediatricians, pediatric nursing and a pediatric phlebotomist;

2. The risks from the DNA banking be minimized by protecting the confidentiality of the subjects by a) the absolute separation of the genetic information from the medical record, b) re-consenting the children when they reach the age of maturity specified by the State, c) providing information about whom to call if the subject wishes to have the DNA removed from the bank and destroyed and d) provision of a statement that the DNA will not be available to the participant later to be used for other purposes; and

3. Clear exclusion criteria are put in place for MRI studies (i.e., testing for implanted metallic subjects, claustrophobia, or the need for procedural sedation).

Direct Benefit

The experts found that there would be no direct benefit for the participants of the proposed research project.

Ethical Principles and Parental Permission and Child Assent

The majority of experts considered that the protocol represented a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health and welfare of children, the investigators had adhered to sound ethical principles and had written excellent recruitment materials, parental permission, and assent forms. The panel was supportive of the plan to re-assent the children at the time of the second research evaluation.

FINDINGS

The majority of the reviewing experts found that the proposed study could be appropriately approved under §46.407, subject to the stipulation that the protocol and consent forms be modified in accordance with the recommendations for further minimization of risks to the children. The majority of experts felt that the research design was sound, offered a reasonable opportunity to further the understanding of an important health risk to children (the prevalence of type 2 diabetes in Japanese-American children and the influence of puberty on metabolism and obesity–related parameters), would be conducted in accord with sound ethical principles, and that adequate provisions were in place to obtain parental permission and child's assent.

One member of the panel did not recommend approval under §46.407. Serious design flaws were cited by this expert, such as:

1) By the researcher's own calculations, only 42 percent of the children to be studied will have reached puberty. This expert believed that the observation period appears to be too short.

2) From the sample size, the statistical probability is that only one subject would ultimately become diabetic. This expert believed that the sample size is too small.

3) Single test determinations may not prove representative of the individual's glucose metabolism or insulin resistance. Therefore, in one expert's opinion this descriptive study will yield little, if any, knowledge about the problem it intends to address. Furthermore, this expert believed that the study would yield little, if any, reliable information that would help to better understand, prevent, or alleviate the serious problem of type 2 diabetes in children.