[January 31, 2008]

The Honorable Michael O. Leavitt
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Leavitt:

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration a set of recommendations relative to Department of Health and Human Services (HHS) human subjects protection regulations at 45 CFR part 46. These recommendations represent the seventh in a series of recommendations from SACHRP.

Background

On October 5, 2004**,** SACHRP approved a resolution establishing a Subcommittee on Subpart A. SACHRP's charge to the subcommittee was to review and assess all provisions of subpart A of 45 CFR part 46 (HHS' codification of the Federal Policy for the Protection of Human Subjects, also known as the Common Rule) and relevant Office for Human Research Protections (OHRP) guidance documents, and based on this review and ongoing assessment, to develop recommendations for consideration by SACHRP in three categories: (1) recommendations on interpretation of subpart A provisions; (2) recommendations for development of new, or modification of existing, OHRP guidance; and (3) recommendations for possible revision of subpart A.

The goals of this review and assessment of subpart A of 45 CFR part 46 are threefold: (1) to enhance the protection of human subjects; (2) to reduce, where possible, regulatory burdens that do not contribute to the protection of subjects in a meaningful way; and (3) to promote scientifically and ethically valid research. To that end, the following recommendations were developed by the Subpart A Subcommittee, and discussed and approved by SACHRP at its meetings on March 30, 2007 and July 30, 2007.

Recommendations Related to Waiver of Informed Consent

1. OHRP should develop guidance on the implementation of the provisions under HHS regulations at 45 CFR 46.116(d) for IRB approval of a waiver or alteration of informed consent requirements. The guidance should emphasize the following general points:
    - This part of the regulations is intended to allow IRBs to waive informed consent in its entirety or any of the required elements of informed consent. IRBs should use this provision for considering a waiver of any or all of the elements of informed consent under HHS regulations at 45 CFR 46.116(a).

- It is important to remember that IRBs must document that a waiver is being applied and how the criteria for a waiver are being met.
- FDA does not have the same criteria for waiver of informed consent that correspond to subpart A. Therefore, if research is subject to FDA jurisdiction, these provisions do not apply.
- The OHRP guidance should also incorporate recommendations 2-6 below.

2. Regarding the criterion under HHS regulations at 45 CFR 46.116(d)(1) for IRB approval of a waiver or alteration of informed consent requirements, IRBs should interpret minimal risk in accordance with SACHRP's recommendations regarding the definition of minimal risk, as approved March 29, 2007.

3. Regarding the criterion under HHS regulations at 45 CFR 46.116(d)(2) for IRB approval of a waiver or alteration of informed consent requirements, in order to determine whether a waiver of informed consent would adversely affect the rights and welfare of subjects, IRBs should consider the following points:
   - Whether there are other federal, state, or local laws that provide rights to potential subjects to require informed consent. IRBs should seek advice from their legal counsel when appropriate to help the IRB with these determinations. This would be especially important for state specific regulations.
   - Whether the subject population, in general, would object if they knew of the waiver and its intent in facilitating research.
   - Whether the subject population, in general, would consider that the waiver has the potential to cause adverse consequences for their welfare or general well being.

   Examples of scenarios where a waiver of consent would adversely affect the rights or welfare of subjects:
   i. The Family Educational Rights and Privacy Act (FERPA; 20 U.S.C. § 1232g; 34 CFR Part 99) is a federal law that protects the privacy of personally identifiable information contained within a student's educational record. FERPA applies to all educational agencies or institutions (K-12 and postsecondary) that receive funds under various programs from the U.S. Department of Education. Generally, educational agencies and institutions must have written permission from the student (or parent if the student is a minor) in order to release any personally identifiable information from a student's education record unless it meets one of a list of specified conditions for which release is allowed. (For example studies to improve instruction conducted by organizations for or on behalf of the educational agency or institution). Other than under such a condition, if an investigator from a local university's college of education requests a waiver of consent to review the educational records (grades and GPA) of students at the university for the past 20 years and maintain identifiers for a research project, the rights granted to students under the federal legislation of FERPA would be violated and the criteria for waiver of informed consent at 45 CFR 46.116(d)(2) could not be met.

ii. In some cultures, the placenta has special meaning and significance, so that waiving consent to use placental samples for research might be interpreted by that community as adversely affecting their rights and welfare.

4. Regarding the criterion under HHS regulations at 45 CFR 46.116(d)(3) for IRB approval of a waiver or alteration of informed consent requirements, IRBs should consider the following points when determining whether research could not practicably be carried out without the waiver or alteration:
   - The commonly accepted definitions of the term "practicable" are (a) feasible; (b) capable of being effected, done or put into practice; and (c) that may be practiced or performed; capable of being done or accomplished with available means or resources.

   It should be noted that this criterion states that the research could not practicably be carried out without the waiver or alteration. Put another way, it would not be practicable to perform the research (as it has been defined in the protocol by its specific aims and objectives) if consent was required. The emphasis being that it is impracticable to perform the research, and not just impracticable to obtain consent. The following concepts may help an IRB determine whether the research could not be practicably carried out without the waiver of consent:

   a) Scientific validity would be compromised if consent was required. Examples of this might include the following:
      i. The sample size required is so large (e.g., population-based studies, epidemiology trials) that including only those samples/records/data for which consent can be obtained would prohibit conclusions to be drawn or bias the sample such that conclusions would be skewed.
      ii. The subjects for whom records would be reviewed are no longer followed and may be lost to follow-up. For example the proportion of individuals likely to have relocated or died may be a significant percentage of the subject population and the research results may not be meaningful and lose statistical power.
      iii. The disclosure of the study purpose as part of the consent process would bias the research subjects so that the results will not be meaningful.

   b) Ethical concerns would be raised if consent were required. For example:
      i. There is a risk of creating additional threats to privacy by having to link otherwise de-identified data with nominal identifiers in order to contact individuals to seek consent.
      ii. There is a risk of inflicting psychological, social or other harm by contacting individuals or families.

   c) There is a scientifically and ethically justifiable rationale why the research could not be conducted with a population from whom consent can be obtained.

d) Practicability should not be determined solely by considerations of convenience, cost, or speed.

5. Regarding the criterion under HHS regulations at 45 CFR 46.116(d)(4) for IRB approval of a waiver or alteration of informed consent requirements, IRBs should consider the following points in determining when it would be appropriate for investigators to provide subjects with additional pertinent information after participation in research for which the requirement for informed consent has been waived:
    - It is important to note that the phrase "whenever appropriate" in this criterion means that, while the IRB must consider if this applies each time a waiver is reviewed, not all protocols which include an informed consent waiver are required to provide additional information to subjects after their participation.
    - This criterion is intended to refer to the need to consider debriefing after research is conducted. In these situations it may be ethically required or determined to be respectful to provide the subject with pertinent information after the research is complete. IRBs may want to consider this mechanism when subjects are included in so-called "deception research," in which some aspects of the study are not fully disclosed upfront so that subject responses are not biased.
    - Under most circumstances, this criterion does not apply to retrospective research conducted under a waiver (e.g., review of existing records).

6. IRBs may find it helpful to use a flowchart that summarizes the criteria under HHS regulations at 45 CFR 46.116(d)(4) for IRB approval of a waiver or alteration of informed consent requirements when considering requests for such waivers. OHRP should revise its decision charts to reflect recommendations in this area, as needed.

Recommendations Related to the Interpretation of Minimal Risk

1. The regulatory intent of minimal risk is to define a threshold of anticipated harm or discomfort associated with the research that is "acceptably-low" or "low enough" to justify expedited review or waiver of consent.

2. The IRB's evaluation of the harms and discomforts of the research should consider the nature of the study procedures, other study characteristics, subject characteristics, and steps taken to minimize risk.

3. In its estimate of research-related risk, the IRB should carefully consider the characteristics of subjects to be enrolled in the research including an evaluation of subject susceptibility, vulnerability, resilience and experience in relation to the anticipated harms and discomforts of research involvement.

4. To satisfy the definition of minimal risk, the estimate of the anticipated harms and discomforts of the research for the proposed study population may not be greater than an

estimate of "the harms and discomforts ordinarily encountered in daily life or during the performance of routine medical and psychological examinations or tests."

5. While the harms and discomforts ordinarily encountered differ widely among individuals and individual populations, an ethically meaningful notion of "harms and discomforts ordinarily encountered" should reflect "background risks" that are familiar and part of the routine experience of life for "the average person" in the "general population." It should not be based on those ordinarily encountered in the daily lives of the proposed subjects of the research or any specific population.

6. In summary, minimal risk should be applied in manner that recognizes that risks are procedure-specific and population-dependent, but that the notion of "acceptably-low" risk is fixed. When the harms and discomforts of the proposed research as they are anticipated to impact the study participants are judged to fall below this acceptably-low risk threshold, the research is said to be "minimal risk."

In addition to the above recommendations related to the interpretation of minimal risk SACHRP approved a series of case studies illustrating the practical application of the above recommendations. SACHRP does not assume OHRP will use any of these examples directly, but believes they illustrate the recommended approach to interpreting minimal risk and may be useful for future guidance development. The series of case studies is provided as Appendix 1 to this letter.

Mr. Secretary, I trust you will find this report acceptable. Your committee members and SACHRP subcommittee members have worked hard in their pursuit of the charges contained in the charter. SACHRP has also worked closely with Dr. Ivor Pritchard and the rest of the OHRP staff and has benefited greatly from their expertise and leadership. We look forward to continuing our work and providing you with recommendations which will enhance human subject protections and advance science for the benefit of all Americans.

Sincerely,

/S/ Samuel Tilden

Samuel Tilden, M.D., J.D., L.L.M.
Chair, Secretary's Advisory Committee on Human Research Protections

cc:
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