Subpart A Subcommittee, SACHRP

Recommendations Regarding the Provisions for Waiver or Alteration of the Informed Consent Requirements Under Department of Health and Human Services (HHS) Regulations at 45 CFR 46.116(d)

A. Background

1. What is the problem? What are the issues we are seeking to address in relation to waiver of informed consent?

Obtaining the informed consent of research subjects prior to their participation is traditionally regarded as a cornerstone for the ethical conduct of research, and a fundamental protection for participants' rights. HHS regulations outline general requirements for informed consent at 45 CFR 46.116, including eight "basic" and six "additional" elements to be addressed when obtaining informed consent.

At the same time, it is recognized that there is valuable research that would be difficult, or impossible, to conduct if consent were required; and that subjects can still be adequately protected in the absence of full consent. Accordingly, the regulations also allow for waiver or alteration of some or all of the elements, as noted in 45 CFR 46.116(d). The waiver allows the interests of subjects to be balanced with societal interests in research, and both will be well served if this regulatory provision is understood and applied appropriately. However, in practice, IRBs may inappropriately utilize this provision for the following reasons:

- Uncertainty in applying criteria (i.e., whether or not to grant the waiver).
- Inconsistency in reviewing the research, including consideration of the waiver of informed consent, owing to variability across IRBs (and institutions). This is especially evident when the waiver provisions are applied in research conducted at multiple sites.
- This uncertainty and variability may lead to underutilization of the waiver, when it may be warranted. Conversely, lack of understanding on how/when to apply may lead to inappropriate application of the waiver, under some circumstances.

2. What do the HHS regulations at 45 CFR 46.116(d) say?

> *An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:*
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> *(1) The research involves no more than minimal risk to the subjects;*
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> *(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;*
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> *(3) The research could not practicably be carried out without the waiver or alteration; and*
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> *(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.*

3. Is there any guidance on interpretation of the provisions of 45 CFR 46.116(d) from the Office for Human Research Protections (OHRP)?

The only guidance that may be found is referenced in the 1993 OPRR (OHRP) Institutional Review Guide Book. It contains the following on pages 3-16 to 3-17:

> *The IRB may approve a waiver of some or all of the consent requirements provided that: (1) the research involves no more than **minimal risk** to subjects [see Guidebook Chapter 3, Section A, "Risk/Benefit Analysis"]; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after they have participated in the study [Federal Policy §__.116(d)]. Most commentators suggest that the IRB also determine whether the knowledge being sought is important enough to justify whatever invasion of privacy may be required either to obtain information about unconsenting (or unaware) subjects or to involve them in research under false pretenses. [See Guidebook Chapter 3, Section D, "Privacy and Confidentiality."]*
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> *Under the Federal Policy (but not FDA regulations), if the research is designed to evaluate or demonstrate possible changes in (or alternatives to) provision of benefits or services provided for under federal, state, or local programs, an IRB may approve alteration or waiver of the consent requirements [Federal Policy §___.116(c)]. If the research could not practicably be carried out without the waiver or alteration of the consent requirements, the IRB may approve such a waiver. Both the **National Commission for the Protection of Human Subjects***

and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research *recommended that such waivers be granted only if subjects will not be denied benefits or services to which they are otherwise legally entitled.*

Record Reviews*. Sometimes, especially in epidemiological studies, scientists need to review thousands of records to identify appropriate subjects for their study. (Consent is not an issue for record reviews of deceased individuals because federal regulations apply only to research involving living human subjects [Federal Policy §___.102(f)].) It is often difficult, if not impossible, to obtain the permission of everyone whose records are contained in the files. For this preliminary part of the research, IRBs will generally waive the consent requirement if: (1) they are satisfied that the information contained in the files is not particularly sensitive; (2) the investigator has devised procedures to protect the confidentiality of the information to be collected; and (3) the study could not practicably be carried out if consent were required. Some university hospitals notify all incoming patients that their records may be reviewed for research purposes; others provide an opportunity to consent (or refuse to consent) to such use.*

B. Recommendations

1. Recommendation 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. Recommendation 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. Recommendation 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 consider that their rights were violated if they knew of the waiver, or 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 of subjects:
    - *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.*
    - *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. Recommendation 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 *(note that some criteria are drawn from "Best Practices for Protecting Privacy in Health Research," published Sept 2005 by the Canadian Institutes of Health Research):*

  (a) Scientific validity would be compromised if consent was required. Examples of this might include the following:

  - *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.*
  - *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.*
  - *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:

  - *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.*
  - *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) Informed consent should never be waived for convenience, nor waived solely for reasons of cost or speed if doing so dilutes the protection of subjects' rights and welfare.

5. Recommendation 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 when determining when it would be appropriate for investigators to provide subjects with additional pertinent information after participation when the requirements for informed consent have been waived:

- It is important to note that the phrase *"when 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 incorporate a debriefing process.
- 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 requirement if:

    - a subject is included in research that exposes them to situations or conditions to provoke a response for research purposes, and the situation would not have ordinarily occurred at that time point (e.g., a debriefing after so-called "deception research" in which some aspects of the study are not fully disclosed upfront); or
    - information is obtained during the course of the research that directly impacts on the safety or welfare of the subject (e.g., a retrospective review of medical charts that revealed something of relevance to ongoing care of patients whose records were included).

6. Recommendation 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.