Appendix B: Recommendations regarding risk in research involving children

The purpose of this internal document is to provide clarification to the recommendations relating to 45 CFR 46.404, 46.405 and 46.406, forwarded by the Subcommittee on Research Involving Children (SRIC), and approved by the Secretarial Advisory Committee on Human Research Protections (SACHRP) on April 18, 2005. To facilitate the review of this document each section (46.404, 46.405 and 46.406) will start with the regulatory language for that part followed by the individual recommendations and relevant discussions. Of note is the fact that all recommendations forwarded by the SRIC and approved by SACHRP provide clarification of existing regulatory language and, hence, do not require changes in the regulations.

Recommendations Related to 45 CFR 46.404: Present Regulatory Language

§46.404 Research not involving greater than minimal risk.

DHHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408

Recommendation/Discussion

1. The definition of "minimal risk" at 45 CFR 46.102(i) when applied to Subpart D should be interpreted as those risks encountered during daily life by normal, average, healthy children living in safe environments or during the performance of routine physical or psychological examinations or tests.

> **Discussion:** SACHRP's intention of this clarification is to emphasize that just because a given population of children live in a less safe environment doesn't provide justification to expose them to greater risk under the minimal risk standard. SACHRP referred to this as a "**Uniform Standard**" and asserts this is consistent with what has been advocated by the National Commission, the Institute of Medicine (IOM) and National Human Research Protection Advisory Committee (NHRPAC). Although "safe environment" was not specifically defined it is clear the committee feels the standard for determining safe environment in all research involving children (including international) should be what is considered a safe environment in the United States. A different standard should not apply to international studies.

2. The evaluation of minimal risk under Subpart D should be indexed to risks in daily life and routine medical and psychological examinations experienced by children the same age and developmental status as the subject population.

> **Discussion:** This second recommendation from SACHRP recognizes the fact the concept of minimal risk should be aged indexed. For example the risks encountered in the daily life of a 2 year old child is significantly different than that experienced by a 17 year old adolescent hence the degree of acceptable minimal risk for any given study population involving children should be adjusted accordingly. So, is this implying that component analysis should be applied to different age groups in the same study?

3. The uniform, age-indexed definition of minimal risk should represent the ***upper*** not lower limits of risk to which children can be exposed under 46.404.

> **Discussion:** The third recommendation recognizes that the amount of risk determined to be minimal for any given population of children (age adjusted) should be the upper limit of acceptable risk for approval under 45 CFR 46.404.

4. Research procedures involving children should be approved as "minimal risk" only if the probability and magnitude of harm are equivalent to or less than the risks of daily life or routine examinations with respect to (1) duration, (2) cumulative characteristics, and (3) reversibility of harm.

Discussion: The fourth recommendation recognizes that any given research procedure thought to be minimal risk does not necessarily need to match the risks encountered in the daily life of normal, average, healthy children living in safe environments or the risks encountered in the procedures conducted during routine childhood examinations but rather be equivalent to the types of procedures done and the level of risks involved. The three areas that an IRB/investigator should consider when determining risk should include the duration of any potential risk, the characteristics of the risk, and the reversibility of the harm.

5. A "routine physical or medical examination" has no precise, universally accepted definition but what is sometimes called a well-child visit offers *one* reasonable basis for comparisons to both, routine medical and routine psychological, examinations or tests.

Discussion: The fifth recommendation provided by SACHRP for 46.404 determinations recognizes the standard "well-child" visit conducted in the United States by most pediatricians and family practice doctors is one of several reasonable benchmarks in defining "routine medical and routine psychological examinations or tests" in children. The following table lists some of the tests and procedures conducted during well child examinations in the United States. The list is not meant to be exhaustive. "Guidance and education" to parents and children includes age appropriate risk counseling such as seatbelt use, tobacco use, and sexual education counseling. This is one way in which to ground what is meant by "daily lives of children". Have any states passed laws about counseling in any of these areas, i.e., sex ed?

Examples of Well-Child Procedures:

- Physical examinations
- Measurements of height, weight, head circumference
- Assessment of obesity with skin fold calipers
- Collection of blood or voided urine
- Measurement of heart rate and blood pressure
- Hearing and vision tests
- Modest changes in diet or schedule
- Testing of fine and gross motor development
- Non-invasive physiological monitoring
- Medical and social history
- Psychological examinations or tests
- Guidance and education interventions (for child and/or parents)
- Index routine psychological tests to standardized screening or assessment measures such as the following: child and adolescent intelligence tests, infant mental and motor scales, educational tests, reading and math ability tests, neurological or motor disorder screening, social development assessment, family and peer relationship assessments, emotional regulation scales, and scales to detect feelings of sadness or hopelessness.

Discussion: The above listed items are examples and any one of these procedures or tests may be greater than minimal risk given the context of the protocol and the population.

6. Research which is conducted under Subpart D outside of the United States should utilize the same uniform standard of minimal risk which is applied in the United States.

Discussion: This recommendation is in many ways another way of emphasizing the concept articulated in recommendation 1 above (Uniform Standard). Specifically, SACHRP agreed that regardless of where any particular research is being conducted the same assessment of minimal risk should apply to all research involving children. Further it is not acceptable to accept a greater degree of risk under the minimal risk

standard just because children in a given foreign country may be exposed to a higher degree of risk in their daily lives. The committee believes this is good public policy.

Recommendations Related to 45 CFR 46.405: Present Regulatory Language

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) the risk is justified by the anticipated benefit to the subjects;
(b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
(c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

Recommendation/Discussion

1. When research presents the prospect of direct benefit for the subject the ceiling on risk is determined by whether it is proportional to the probability and magnitude of benefit.

Discussion: The intention of this recommendation is to stress the balance that must be made between level of acceptable risk and amount of expected benefits from any given study or procedure. Specifically the amount of acceptable risk should represent a ceiling for which no further risk would be acceptable given the probability and magnitude of the benefit. In making this **assessment the IRB needs to consider what is the expected chance for benefit and how large of a benefit is expected. So the concept of acceptable risk is a sliding scale where acceptable risk may increase with expected benefits.**

2. As an additional protection, even if the risks are balanced by the anticipated benefits, a study may not be independently approved by an IRB if the anticipated benefits are not at least as favorable to the subjects as available alternative approaches.

Discussion: The intent of this recommendation is to provide clarification on how to balance the risk benefit analysis of the protocol intervention with the known benefits of alternative treatments. The committee agrees that the investigator and the **IRB should consider the benefits from approved or standard therapy that are being forgone by the use of the investigational treatment. If the expected benefits of the investigational therapy are not as good as the standard therapy then the research should not be approved under 45.405.**

3. The evidentiary basis for the risk-benefit decision should be scientifically sound to justify undertaking whatever risk is involved.

Discussion: As with other approval categories the nature of **the data supplied by the investigator to the IRB** to support their risk benefit analysis should be scientifically sound and represent a body of evidence. The point is that opinions about risks and benefits should be based on evidence not on an investigator's hunch. The evidence could include data from adults and animals.

4. **Relative to monitoring procedures:** any benefit of monitoring listed in a 46.405 application must be an objective of the study and for approval under 46.405; the monitoring procedure must have the intended, not incidental, potential benefit of influencing the management of the individual child's disease.

Discussion: This recommendation is intended to clarify when a monitoring procedure can be considered a benefit. Specifically the committee agrees that any benefit of monitoring must be a stated objective of the protocol. For approval under 46.405 the monitoring procedure must have the intended, not incidental, potential benefit of influencing the management of the child's diseases or condition. Ultimately it is not acceptable to "piggy back" additional procedures of greater than minimal risk in a protocol under the guise of it being a monitoring procedure necessary for the child's care. **For example the** taking of an additional biopsy that is not clinically indicated cannot be justified by the fact that it might demonstrate some undetected problem. Additionally, the use of an MRI to study brain activity in children with ADHD cannot be justified by stating that the MRI could potentially provide benefit to the child by finding occult tumors.

5. Each research procedure in a treatment study must be evaluated independently in terms of potential benefits and risk to the subject **(i.e. component analysis).** Different procedures in a single trial may be approved or disapproved under different Subpart D standards.

Discussion: The purpose of this recommendation is to provide guidance on how IRBs should review multiple procedures in a given protocol. SACHRP believes that **IRBs should avoid reviewing multiple procedures in a single protocol as a package plan but rather should review the risks and benefits of each procedure and intervention individually as well as collectively**. After careful review of each procedure and intervention it may become apparent that different procedures and interventions **can be approved under different subpart D categories.** The committee felt this would add additional protections to children participating in research. Procedures offering no prospect of benefit to the subject should not be approved under 46.405. For example an imaging procedure with greater than minimal risk used to assess dose-response in a tumor protocol involving children cannot be approved under 46.405 unless the investigator can provide sufficient information to support that knowing the dose-response at that given time will affect clinical decisions that might benefit the subject. **More simply, the intention of the committee is to make IRBs and investigators think about the merits of each procedure and intervention individually**. Extra procedures that offer the subject no additional benefit should be minimized, especially if they present any level of risk greater than minimal. Procedures that offer no benefit to the subject but are important to the research, such as providing scientific validity, should be considered under 46.406.

The committee realizes that this recommendation may be labor intensive for the IRB but agreed that it should be required. Further, the committee agreed that the primary investigator should have the responsibility to present supporting information for each procedure and intervention in any given protocol in a clear and concise manner to facilitate review. The following table provides a suggested format in which the investigator can provide the details required by the IRB to conduct a component analysis:

Research Procedure	**Prospect of Direct Benefit**		**No Prospect of Direct Benefit**		
	Intervention	Monitoring	404: Minimal Risk	406: Minor Increase over Minimal Risk	407: Requires HHS Secretary Approval

6. The responsibility to demonstrate to the IRB which procedures do or do not have the prospect for direct benefit is *the responsibility of the investigator.* If procedures without the prospect of direct benefit are included in a treatment trial, investigators and IRBs should consider an **opt-out provision** for those procedures. However, if the research cannot be reasonably conducted without procedures with no clinical relevance for the child's treatment, and the procedures represent no more than a minor increase over minimal risk, the informed consent must clearly explain the nature and rationale for such procedures. **To avoid family exploitation, IRBs should require strong evidence that the protocol cannot be conducted without each of the non-beneficial procedures**.

Discussion: This recommendation goes along with recommendation 5 and provides clarification as to the responsibility of the investigator relative to procedures that offer no direct benefit to the subject. The committee believes when a research protocol includes procedures that offer no direct benefit to the subject and is not directly relevant to the aims of the protocol, the IRB and the investigator should consider offering subjects and parents the opportunity to opt out of the procedure. For example subjects and parents should be permitted to opt out of the collection of extra biopsies that are being collected for future studies and have no relevance to the immediate protocol aims. Additionally, if the research cannot be reasonably conducted without the non-beneficial procedures and the procedures represent no more than a minor increase of a minimal risk, the informed consent must clearly explain the nature and rationale for such procedure. The informed consent should clearly state which procedures are being done purely for research purposes and which procedures provide clinical benefit. To avoid subject and family exploitation **the IRB should require strong evidence that a research protocol cannot be conducted without each of the non-beneficial procedures.**

7. **Final comment on 46.405**

Studies that could be included under 46.405 could include phase I pharmacokinetics studies provided several conditions are met. For example, a phase I pediatric cancer protocol with greater than minor increase over minimal risk could potentially be approved under 46.405 if enrolled subjects had failed alternative treatments and the intervention offered some potential for benefit, providing the risks are proportional to the benefits. Toxicity and benefits would have to be supported by adults and/or animal studies.

Recommendations Related to 45 CFR 46.406: Present Regulatory Language

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) the risk represents a minor increase over minimal risk;
(b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
(c) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
(d) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

Recommendation/Discussion

1. Criteria for "minor increase over minimal risk" should include the following:
   (a) The procedure does not meet minimal risk criteria

   (b) The investigator has presented sufficient evidence about the procedures, population, and the qualifications of research personnel to assure the IRB that:
   - The increase in the probability and magnitude of harm is only slightly more than minimal risk.
   - Any potential harms associated with the procedure will be transient and reversible in consideration of the nature of the harm (restricted to time of procedure or short post-experimental period).

- There is no or an extremely small probability that participants will experience as severe the potential pain, discomfort, stress, or harm associated with the procedure.

Discussion: The intent of this recommendation is to provide clarity to the phrase "minor increase over minimal risk". After much effort to provide concrete examples and a long list of criterion in which to judge whether a procedure or intervention represented a minor increase over minimal risk, the committee agreed to these criterion.

The first criterion of not meeting the criteria for minimal risk is self-explanatory.

The second group of criteria is more involved and requires *the investigator* to provide to the IRB sufficient evidenced-based information that enables the IRB to assess risk. Specifically the investigator should provide sufficient evidenced-based information to the IRB so that they may conclude that the probability and magnitude of harm is only "*slightly more than minimal risk"*. Another way of thinking about this is that the chance of harm and the degree of harm should only be a "little bit more" than that meeting the definition of minimal risk. Additionally information should be provided by the investigator that supports the judgment that any potential harms would be transient and reversible (with or without medical intervention). This information could include information such as the qualifications of the individual performing the procedure and data on the experience of similar populations with the procedure. The committee recognizes that in many cases it is impossible to exclude all chances of severe adverse events however they believe the investigator should provide sufficient evidenced-based information that supports the judgment that the probability an adverse event will be reported as severe by the subject is small. It is important to note the threshold for "sufficient evidence" should be greater than relying on the opinion of the investigator. This is not to say that the experience level of the investigator should not be considered. For example an IRB could conclude that a spinal tap done by an experienced physician with many documented cases without problems is a minor increase over minimal risk whereas a spinal tap conducted by a novice intern would be greater than a minor increase over minimal risk. Likewise, the nature of the setting should also be considered. For example a spinal tap conducted in an emergency department that is adequately staffed and equipped for emergencies is generally considered safer than a spinal tap conducted in an office setting.

2. The term condition should be interpreted as referring to a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific or clinical evidence has shown to negatively affect children's health and wellbeing or to increase their risk of developing a health problem in the future.

Discussion: The intention of this recommendation is to provide clarity to the term condition. In defining this term the committee wanted to distinguish between what an established "*body of evidence"* supports as a condition to what is clinically believed to be a condition. The two are not always the same and the committee wanted to not permit the approval of research under 46.406 based on a "*hunch of clinical evidence*". The committee felt that there must be some objective data to support the notion that the condition proposed for study has been shown to negatively affect children's health and wellbeing or to increase the risk of developing a health problem in the future. For example studies that evaluate hypothetical predispositions to diabetes can be approved under 46.406 provided there is sufficient scientific or clinical evidence to link the condition (hypothetical predisposing factor) to the event (diabetes). Basically there has to be some grounds or reasonable rationale to expose children to potential harm that is greater than minimal risk.

The committee also recognizes there are times when a cohort of normal healthy children may be considered as having a condition appropriate for research under 46.406. For example, it is reasonable for an IRB to determine that a group of healthy pre-school children have a condition necessary to study the immunogenicity of a potential vaccine for a common childhood disease. Although the children are healthy they have the condition of being a child at risk for the common disease under study. Whereas the same cohort of children would not have a condition sufficient to meet the requirements to be enrolled in a protocol to test the pharmacokinetics of a drug for the potential treatment of childhood leukemia since the event (childhood leukemia) is not common in children. Further the committee agrees that healthy children

living in areas where the risk of a serious disease or adverse life events is high, may be determined by an IRB to have a condition necessary to be enrolled in a protocol designed to discover factors that may lead to an increased understanding or amelioration of the serious disease or adverse life situation/condition. **For example,** it would be reasonable to approve a malaria vaccine safety protocol under 46.406 on healthy children living in an area where malaria is endemic (presuming the risk was determined to be no more than a minor increase over minimal risk). In this case the condition would be living in an environment where the risk for malaria is high.

3. For interventions or procedures to be considered of "vital importance" there must be clear and significant scientific evidence that their use is likely to yield generalizable knowledge that would contribute to understanding the etiology, prevention, diagnosis, pathophysiology, amelioration or treatment of a condition or disorder.

Discussion: The intention of this recommendation is to provide clarity to the phrase "vital importance". The concern is that most investigators, irrespective of the protocol, honestly believe that their protocol addresses an issue of vital importance. It is the committee's feeling that the threshold for accepting something as vitally important should be higher than blindly accepting the beliefs of the investigator. The committee agrees that the principle investigator must supply to the IRB sufficient evidence to support the investigator's belief that the protocol evaluates something that is vitally important to children and will contribute to knowledge about the disorder or condition. The supporting data provided needs to be clear and evidenced based. The primary goal of the proposed protocol should contribute to understanding the etiology, prevention, diagnosis, pathophysiology, amelioration or treatment of the disorder or condition. The determination of what evidence is "clear and significant" is a subjective analysis that must be deliberated by the IRB.

An important concept to understand is when can a healthy normal control group be included in a protocol approved under 46.406? Although several factors need to be considered, relative to "vital importance", a cohort of normal healthy children could be approved if the research is designed to collect data that are vital to understanding the healthy comparison's group condition. For example a research program that proposes to compare the biological markers between HIV negative and HIV positive newborns born to HIV positive mothers could be approvable under 46.406 if the research is also designed to further understand factors contributing to healthy neonate's natural immune response against maternal HIV. In this case the condition for the healthy controls would be "not being infected despite having an HIV positive mother". In this case, it could be clearly argued that the data from the HIV negative newborns is vitally important information about their condition. Whereas a research proposal that includes a healthy control cohort primarily to improve the scientific validity of the protocol and not answer something vitally important about the control would not be approvable under 45.406.

4. In applying the commensurate criteria IRBs should determine that research interventions or procedures are reasonably similar to those procedures and interventions that children with the condition or disorder as a class have or are expected to experience. Commensurate should not be introduced to gauge the acceptable level of risk. Under 46.406 the level of acceptable risk is determined by the definition of "minor increase over minimal risk". The commensurate criterion mean that some children may not be permitted under 46.406 to experience even a minor increase over minimal risk, either because of their or their parents/guardians' unfamiliarity with the procedure, or the research imposes an unfair burden on the subject.

Discussion: The intention of this recommendation is to clarify the difficult and controversial concept of commensurate. The committee feels that commensurability should only apply to the informed consent (parental permission/child assent) process. Specifically, commensurate should not be introduced to gauge the acceptable level of risk to which children can be exposed to in a given protocol. Under 45 CFR 46.406 the level of risk should be determined under the "minor increase over minimal risk" standards discussed above.

The following example exemplifies the type of deliberations that an IRB should conduct in order to approve a protocol under 45 CFR 46.406 using the four criteria described above.

5. A protocol proposes to evaluate the time course and mechanism of insulin resistance in obese children who are believed to be at risk for developing Type II Diabetes. The children are otherwise healthy but would have the condition of "being at risk for diabetes". Although most clinicians would agree that there is "clear and significant scientific evidence" to support the link between obesity and the development of diabetes, it would be the investigator's responsibility to present scientific evidence to support this position.

In this protocol each subject will have an insulin clamp attached to one arm and an intravenous solution containing glucose in the other arm (essentially two intravenous infusion solutions). Various amounts of insulin and glucose would be infused over a four hour period in order to assess how each compound is handled by the body. Overall, most IRBs would agree that the procedure does not meet the minimal risk criteria because there is a risk of hypoglycemia, dizziness and fainting with the infusion of insulin. The investigator would have to provide a reasonable argument with supporting evidence that the risks involved with the procedure are only "slightly greater" than minimal, with the baseline for minimal being the risk of daily life of children living in safe environments or during the performance of routine examinations or tests for obese children (criterion 1). However in order to satisfy criterion 1 the investigator must further provide sufficient evidence about the procedure to assure the IRB that the probability and magnitude of harm is only slightly more than minimal risk (example, risk of hypoglycemia is 1:500), any potential harms are transient and reversible (hypoglycemia is readily treatable with glucose), and that the procedure is unlikely to be experienced as severe relative to pain, discomfort, stress or other harms. In order to allow the IRB to determine that the risks of hypoglycemia are transient and reversible the investigator should provide information such as how subjects will be monitored for hypoglycemia, how quickly would the hypoglycemic state be detected, and how would hypoglycemia be treated.

Relative to vital importance (criterion 3), the investigator would need to present to the IRB sufficient information about how this information learned from this protocol would help obese children as a class in the future and would contribute to generalizable knowledge that would contribute to the understanding and prevention of the development of diabetes in obese children. Finally, relative to "commensurability (criterion 4) the investigator would need to provide an argument that the procedures are reasonably similar to those procedures and interventions that children with the condition or disorder as a class have or are expected to experience. The intravenous infusion of glucose could be compared to a vaccine injection or simple blood tests that obese children get as part of their well child examinations. Further it could be reasonably argued by the investigator, since obese children as a class are at risk of developing diabetes they would be expected to experience interventions such as insulin pumps and insulin clamps in the future (assuming they develop diabetes).

A healthy, non-obese cohort of children would not be approvable under 46.406 for this insulin clamp protocol because they would not have the condition of "being at risk for developing diabetes". A cohort of obese children with autism would not be approvable under 46.406 for this insulin clamp protocol because they would most likely experience the invasive procedures of the insulin clamp and intravenous glucose as very stressful and potentially severe.? Criterion 1 would, therefore, not be satisfied. **Finally, it is important to note that each of these criteria are independent and that the level of risk is not to exceed a minor increase over minimal risk regardless of the commensurate experience of the selected population. The degree of risk should be determined prior to evaluating any other criterion.**

Note: Although not a recommendation of SACHRP the general feeling was that the regulations at 46.406 represent a ceiling on the level of risk and subject population an IRB can independently approve for pediatric research with no prospect of direct benefit. Proposed research in children which pose more than a minor increase over minimal risk without the direct benefit for children with a condition or disorder or present only a minor increase over minimal risk for a healthy control should be referred to OHRP for a 407 determination.

Related Letters

July 28, 2005 SACHRP Chair Letter to HHS Secretary Regarding Reco