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Report from NHRPAC

Clarifying Specific Portion of 45 CFR 46 Subpart D that Governs Children's Research

This report is written to clarify a small portion of the federal regulations that governs research involving children, specifically the interpretation of the concepts of "minimal risk" and "minor increase over minimal risk" described in sections §46.404 and 46.406. It is hoped that the report will result in the creation of informative guidance from OHRP in order to assist institutional review boards (IRBs) and investigators to understand these concepts better and use them in a more consistent manner in their deliberations. Future reports from the Children's Workgroup will deal with other aspects of the regulations including research that offers the prospect of direct benefit to the individual participant as described in section §46.405 of the federal regulations.

Minimal risk

The Common Rule for the protection of human subjects of research (45 CFR 46) includes a definition of minimal risk:

> *§46.102*
> *(i) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*

Research studies that involve children are permitted if the local IRB finds that the level of risk is no greater than minimal regardless of whether the research offers the prospect of direct benefit to the child (§46.404). Ever since these regulations have been promulgated there has been considerable discussion as to the application of the minimal risk standard.

We interpret the definition of minimal risk to be that level of risk associated with the daily activities of a normal, healthy, average child. Risks include all harms, discomforts, indignities, embarrassments, and potential breaches of privacy and confidentiality associated with the research. Conceptually, the minimal risk standard defines a permissible level of risk in research as the socially allowable risks which parents generally permit their children to be exposed to in non-research situations. Healthy children, ranging from newborns to teens, experience differing levels of risk in their daily lives. Indexing the definition of minimal risk to the socially allowable risks to which normal, average children are exposed routinely should take into account the differing risks experienced by children of different ages.

If certain groups of children are routinely exposed to greater risks as part of their ordinary lives because of the circumstances in which they live, their level of increased risk ought not be interpreted as minimal risk just because it is part of the common experience of these otherwise healthy children.

In interpreting the phrase *"ordinarily encountered in the daily life or during the performance of routine physical or psychological examinations or tests,"* IRBs need not limit the tests or procedures in the research to those actually used in routine physical or psychological evaluations. The interpretation of whether the level of risk is minimal should be one of "equivalence of risk." A test or procedure which entails minimal risk is one for which the probability and magnitude of harm associated with the test or procedure is equivalent to and no greater than the risk of events ordinarily encountered in the daily life of a normal, healthy, average child, or the socially allowable risks parents permit their normal, healthy, average children to be exposed to in their ordinary lives.

Participation in research must be voluntary. Investigators and IRB members should remember that even if the research presents only minimal risk to the child there is no obligation to participate. The child (when appropriate) and his/her parent(s) ultimately determine what level of risk is acceptable and whether they choose to participate in a specific research study. This requires that the IRB ensure that the informed consent process makes clear that there is no prospect of benefit to the individual participant, and that the assent and permission are voluntary and uncoerced with no implication of obligation to be part of research even if the risk is minimal.

Minor increase over minimal risk

The federal regulations governing research with children permit research involving greater than minimal risk and no prospect of direct benefit to individual children, but likely to yield generalizable knowledge about the child's disorder or condition under certain very specific circumstances.

> *§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.*
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> *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.*

This category of permissible research was proposed by the National Commission for the Protection of Human Subjects of Biomedical Research in its 1977 report "Research Involving Children" and integrated into the final federal regulations in 1983 in order to allow research of vital importance that would not otherwise be permissible concerning diseases, disorders, or conditions that affect children. These regulations impose a significant limit on the discretion of parents to permit the participation of their children in research that entails more than minimal risk without the prospect of direct benefit, but at the same time, the regulations do permit important research for the long-term benefit of children.

IRBs are responsible for determining what level of risk constitutes a minor increment over minimal. In making the determination, IRBs should only permit risks that are a little more than minimal and pose no significant threat to the child's health or well-being. While the definition of minimal risk is indexed to the risks encountered in the daily lives of normal, healthy, average children, the permissible level of risk associated with a minor increase over minimal should be just a bit more than that level and also commensurate with the risks of interventions or procedures having been experienced or expected to be experienced in the lives of children with a specific disorder or condition. This concept of commensurability is important to allow the child and parents to have a basis upon which to make thoughtful judgments about assent and permission. The fact that children may experience invasive procedures with considerable risk and discomfort during the care and treatment of a disease does not justify risks greater than a minor increase over minimal in a research study that provides no prospect of direct benefit to the individual subjects.

It is the obligation of each investigator to provide the evidence, and the task of the IRB to concur that this level of risk is necessary in order to yield generalizable knowledge of vital importance for the understanding of the participants' disorder or condition. In making the determination as to the level of importance of the research, the IRB must be convinced that the information generated from the research has substantial promise of contributing to the understanding or amelioration of the participants' disease, disorder or condition.

A controversial issue in permitting research based on this section of the regulations is interpretation of the definition of "disorder or condition." The National Commission used the word "condition" to refer to situations that may "jeopardize the health of children, interfere with optimal development, or adversely affect well-being in later years." The phrase "disorder or condition" refers to a characteristic of the group of potential research subjects, and implies that this characteristic can be understood more broadly than simply a specific disease or diagnostic category.

We interpret the concept of disorder or condition as relating to a specific characteristic which describes a group of children, a physical, social, psychological, or neuro-developmental condition affecting children, or the risk of certain children developing a disease in the future based on diagnostic testing or physical examination. Thus, for example, prematurity, infancy, adolescence, poverty, living in a compromised physical environment, institutionalization, or having a genetic predisposition to future illness are some of the disorders or conditions of children that can, under the appropriate circumstances, warrant permissible research that presents levels of risk that are a minor increase over minimal without the prospect of direct benefit.

Amelioration of risk

In determining whether a proposed test or procedure is consistent with minimal risk or a minor increase over minimal risk, investigators and the IRB should take into consideration the context in which the research will be performed. The IRB must learn about the populations that will be potential subjects of the research, taking into account social and cultural factors that may increase or decrease the level of risk for specific groups. In addition, the experience of the investigator and research team as well as the setting of the research may influence the level of risk experienced by the subjects. In some settings an IRB might consider certain risks as a minor increase over minimal while the same risks in another setting would be more than a minor increase over minimal.

It is the duty of the investigator and the IRB to ensure that risks are minimized in all research. Thus, even in research studies that have risks deemed minimal, or a minor increase over minimal, every attempt should be made to minimize risks. For example, procedures should only be performed by professionals skilled with children, protocols should include specific rules setting limits on the number of attempts at a procedure or the length of time for completion of a questionnaire. In addition, appropriate methods should be used to orient the child to the research and decrease potential anxiety and discomfort, and explicit plans should be developed to protect subjects from breaches of privacy and confidentiality.

The following tables and examples are meant to help efforts in human research protection and to assist investigators and IRBs involved in research with children, but are not intended to provide definitive guidance. Levels of risk for a specific research proposal must be evaluated based on the actual risk of the proposed procedures and interventions, the context of the research, and the population studied. Levels of risk will also vary depending on the characteristics of individual subjects and the skill and experience of investigators.

Table I lists procedures that are commonly included in research studies involving children. For each procedure the category of risk for a single procedure is suggested. Multiple or repetitive procedures may change the level of risk for any of these procedures.

Table II lists additional common procedures used in research involving children with some explanation of the varying determinants of level of risk dependent on the context of the procedures.

Table I: Common procedures and category of risk

PROCEDURE*	CATEGORY OF RISK	
	MINOR INCREASE OVER MINIMAL	MORE THAN A MINOR INCREASE OVER MINIMAL

	MINIMAL		
Routine history taking	X		
Venipuncture/fingerstick/heelstick	X		
Urine collection via bag	X		
Urine collection via catheter		X	
Urine collection via suprapubic tap			X
Chest xray	X		
Bone density test	X		
Wrist xray for bone age	X		
Lumbar puncture		X	
Collection of saliva	X		
Collection of small sample of hair	X		
Vision testing	X		
Hearing testing	X		
Complete neurological exam	X		
Oral glucose tolerance test	X		
Skin punch biopsy w/topical pain relief		X	
Bone marrow aspirate w/topical pain relief		X	
Organ biopsy			X
Standard psychological tests	X		
Classroom observation	X		

***** The category of risk is for a single procedure. Multiple or repetitive procedures are likely to affect the level of risk.

Table II: Interpreting level of risk in common procedures

PROCEDURE	DETERMINANTS OF LEVEL OF RISK
Indwelling heparin lock catheter	• The level of risk may range from minimal to more than a minor increase over minimal depending on: age of the child, length of time catheter will be in place, number and volume of samples, and setting of the research
Single SC or IM injection	• The level of risk of a single injection may range from minimal to more than a minor increase over minimal depending on the substance injected
Nasogastric tube insertion	• Generally minor increase over minimal risk but should be commensurate with prior experience of the child in order to provide adequate assent and permission
Small amount of additional tissue obtained at surgery	• Generally minor increase over minimal risk but must take into account any increased operative time, the specific organ or tissue, and the likelihood of bleeding and infection
MRI	• If no sedation – generally minimal • If procedural sedation – generally minor increase over minimal. Intubation in the appropriate setting may decrease potential risks for certain children and its possible use should be considered on a case by case and proposal by proposal basis.
Psychological test / survey/ interview / observation	• Generally minimal if performed under standardized conditions but the level of risk may increase depending on the sensitive nature of questions, the possibility to trigger unpleasant memories or emotions, and the length of the instrument or observation

Example 1. Predisposition to diabetes

Children who are obese are at greater risk than normal weight children of developing Type 2 diabetes, associated with resistance to the physiologic action of insulin. Research scientists may propose to examine the time course and mechanism of insulin resistance in obese children who are otherwise healthy. Such studies might use various procedures to assess insulin resistance. These tests would not meet the criteria of minimal risk procedures because the risks and discomforts associated with the tests are greater than ordinarily encountered in the daily lives of normal, healthy, average children.

However, obesity can be considered a condition that warrants study because of its association with the development of Type 2 diabetes and other serious diseases. Thus, if the IRB determined that the proposed study was likely to yield generalizable knowledge of vital importance about the development of diabetes or the pathophysiology of obesity, that the risk of the procedures performed in the proposed study represents a minor increase over minimal and are commensurate with expected experiences of the subjects, and that the site for the study and the skill and experience of the investigator were appropriate, the study could be approved within 45CFR §46.406, research involving greater than minimal risk and no prospect of direct benefit.

Example 2. Neonatal drug metabolism

Neonates metabolize drugs at rates that differ substantially from older children and adults. Research scientists might propose to examine the activity of neonatal drug metabolizing enzymes using a small dose of dextromethorphan administered orally followed by the measurement of timed blood levels. Dextromethorphan is a drug commonly used as a cough suppressant and is not prescribed in neonates. An IRB might consider the administration of dextromethorphan to a neonate not to meet the criteria for minimal risk research.

However, being a neonate can be considered a condition that warrants study because of the importance of understanding this developmental phase of childhood. The IRB could find the proposed study permissible within 45CFR §46.406 if the dose of dextromethorphan was so small as to be physiologically inactive and the research procedures were assessed to be consistent with a minor increase over minimal risk and the other necessary aspects of 45CFR §46.406 were fulfilled.

Example 3. Behavioral and social science research

Integrating children with school behavioral problems into a normal classroom is a challenge for teachers and school administrators. Social and behavioral science researchers might propose to do psychological testing of children designated by their teachers as having behavioral problems in order to understand better the causes of problem behaviors and to propose interventions to improve academic performance and interpersonal relationships. This group of children could be considered to have a condition worthy of study.

The level of risk associated with such testing might be considered to be minimal and therefore permissible under 45CFR§46.404. If the IRB determined that the level of risk was a minor increase over minimal, the proposal could still be permissible if it fulfilled the criteria of 45CFR§46.406.

Example 4. Examining risk of recurrence in leukemia

Children with acute lymphoblastic leukemia (ALL) have a very good prognosis for cure with intensive treatment, but some children do relapse over time. Clinical researchers might propose to do serial bone marrow aspirates every month during the course of the first year of treatment of children with ALL to examine changes in bone marrow cell molecular characteristics during and after chemotherapy in order to develop greater understanding of the dynamics of the suppression and re-population of the bone marrow. Most of the proposed bone marrow aspirates would not be clinically indicated but might provide additional scientific information of importance.

Children with ALL could be considered as having a condition that warrants investigation and bone marrow development during and after chemotherapy is an important topic for study, but because there is no prospect of direct benefit of the additional bone marrow aspirates and the level of risk and discomfort of this number of serial aspirates exceeds a minor increase over minimal, this proposal should be rejected by the IRB as not permissible under 45CFR§46.406. Even if there might be some children who would be willing to assent and some families who would be willing to give permission for such a study, the IRB should not permit it to proceed as proposed.