DAIDS
Bethesda, MD USA

POLICY

Policy for Enrolling Children (including Adolescents) in DAIDS-Funded and/or Sponsored Human Subject Clinical Research: Protocol Document Requirements

Approval Date: Pending No.: DRAFT

1.0 PURPOSE

The purpose of this policy is to describe the special contents required in protocols of DAIDS-funded and/or sponsored human subjects clinical research that include children. The requirement to submit these contents in sufficient detail to the approving Institutional Review Board (IRB)/ Ethics Committee (EC) will assist the IRB/EC in ensuring that the study is reviewed and conducted in accordance with applicable U.S. Federal laws and regulations.

2.0 SCOPE

This policy applies to all DAIDS-funded and/or sponsored human subject clinical research that intends to enroll children (including adolescents) in clinical research.

3.0 BACKGROUND

DAIDS-funded and/or sponsored human subject clinical research may involve children in the U.S. and, increasingly, children who reside in international settings. A significant portion of DAIDS-funded and/or sponsored human subject clinical research includes multi-center and network studies requiring centralized development of study (protocol) documents that are subsequently reviewed by multiple IRBs/ECs at diverse institutions. In order to ensure that DAIDS-funded and/or sponsored human subject clinical research is in compliance with all applicable laws and regulations governing the enrollment of children, DAIDS has established requirements for protocol content and requirements for clinical research sites to maintain written site policies and procedures. This policy describes the protocol document requirements. A companion policy, *Policy for Enrolling Children (including Adolescents) in DAIDS-Funded and/or Sponsored Human Subject Clinical Research: Clinical Research Site Requirements,* describes required written site policies and procedures and responsibilities of the Protocol Team, IRB/EC, and the Principal Investigator (PI).

U.S. Regulatory Requirements

In addition to 45 CFR 46.111 *Criteria for IRB Approval of Research* and 21 CFR 56.111 *Criteria for IRB Approval of Research*, U.S. Federal regulations governing research in human subjects identify children as a vulnerable population and mandate additional scrutiny and protections prior to their involvement in research. These additional requirements found in 45 CFR 46 Subpart D and 21 CFR 50 Subpart D are described in this policy.

Categories

Three of the four categories of human research involving children may be approved by an IRB/EC. The four categories differ from one another according to the level of risk involved, the prospect of direct benefit to the research participants, and the anticipated research findings. For all four categories, the proposed research activity must satisfy the requirements for parental or guardian permission and child assent. Depending on the category, additional conditions must be met in order for the IRB/EC to approve the research activities (see Appendix 1).

4.0 DEFINITIONS

Advocate: An individual who has the background and experience to act in, and agrees to act in, the best interests of the child throughout the duration of the child's participation in the research and who is not associated in any way (except in the role as an advocate or member of the IRB/EC) with the research, the investigator(s), or the guardian organization. 45 CFR 46.409(b)

Assent: A child's affirmative agreement to participate in research. Mere failure to object should not, absent of affirmative agreement, be construed as assent. 45 CFR 46.402(b) and 21 CFR 50.3(n)

Children: Persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted. 45 CFR 46.402(a) and 21 CFR 50.3(o)

Clinical Investigation: Any experiment that involves a test article and one or more human subjects and that either is subject to the requirements for prior submission to the Food and Drug Administration (FDA) under section 505(i) or 520(g) of the act, or is not subject to the requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. 21 CFR 50.3(c)

DAIDS sponsored: DAIDS is responsible for the management (including submission of the Investigational New Drug Application (IND) to the Food and Drug Administration (FDA) and the initiation of the study) and oversight for the clinical trial or study.

DAIDS funded: DAIDS is providing financial support for the clinical trial or study.

Family Member: Any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of

brothers and sisters; and any individual related by blood or affinity whose association with the subject is the equivalent of a family relationship. 21 CFR 50.3(m)

Federalwide Assurance (FWA): The Federalwide Assurance (FWA) is the only type of assurance of compliance accepted and approved by the Office for Human Research Protections (OHRP) for institutions engaged in non-exempt human subjects research conducted or supported by the U.S. Department of Health and Human Services (DHHS). Under an FWA, an institution commits to DHHS that it will comply with the requirements set forth in 45 CFR 46, as well as the Terms of Assurance (see http://www.hhs.gov.ohrp/humansubjects/assurance/filasurt.htm). (OHRP)

Guardian: An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. 45 CFR 46.402(e). An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. 21 CFR 50.3(s)

Minimal Risk: 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. 45 CFR 46.102(i) and 21 CFR 50.3(k)

Parent: The child's biological or adoptive parent. 45 CFR 46.402(d) and 21 CFR 50.3(p)

Permission: The agreement of parent(s) or guardian to the participation of their child or ward in research. 45 CFR 46.402(c) and 21 CFR 50.3(r)

Principal Investigator (PI): The qualified person designated by the applicant institution to direct the research. PIs oversee the scientific and technical aspects of a grant and the day-to-day management of the research. (NIAID)

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. ICH E6 1.44

Protocol Team: A team of individuals comprised of grantees, investigators, statisticians, and other protocol support personnel who work to develop concepts into DAIDS-funded and/or sponsored research studies. DAIDS medical officers maybe involved as members of this team. (DAIDS)

Ward: A child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law. 21 CFR 50.3(q)

For additional definitions see DAIDS Glossary

5.0 RESPONSIBILITES

5.1 The Protocol Team is responsible for providing sufficient detail in the protocol document to allow for the performance of a risk/benefit analysis and an assessment of the need for child assent.

5.2 The IRB/REC identified on the Federalwide Assurance of the institution where the research will be conducted is responsible for the review of all clinical research enrolling children, determining if risks to subjects (in this case, children) are reasonable in relationship to anticipated benefits (in accordance with U.S. 45 CFR 46.111 and Subpart D; 21 CFR 50, Subpart D, 21 CFR 56.109; 21 CFR 56.111(2), and making the determination that adequate provisions for soliciting the assent of the child and permission of participants' parents or guardians are in place (as set forth in 45 CFR 46.408 and 21 CFR 50.55). The IRB/REC is responsible for determining when each child or the children are capable of assent, when assent is not necessary or can be waived, and communicating its findings to the investigator. 45 CFR 6.408(a)

5.3 The Principal Investigator (PI) is responsible for ensuring that written policies and procedures are developed and maintained at the clinical research site that ensure that the enrollment of children into clinical research is consistent with applicable laws and regulations regarding initial and ongoing parental or guardian permission and child assent, that such procedures are in compliance with local institutional and IRB/EC policies and procedures, and that they are consistently applied. The PI is also responsible for ensuring that DAIDS is informed of the IRB/EC determinations including risk/benefit analysis, IRB/EC approval of studies and amendments, and decisions regarding the need for child assent.

6.0 POLICY

In order to ensure that the requirements of 45 CFR 46 *Subpart D Additional Protections for Children Involved as Subjects in Research* and 21 CFR 50 *Subpart D Additional Safeguards for Children in Clinical Investigations* are satisfied, the Protocol Team will provide, in a section of the protocol, the following information required for the IRB/EC to review and approve the protocol.

6.1. A description of the research activities in sufficient detail for the IRB/EC to determine into which of the four categories the research activity falls (see Appendix 1);

6.1.1 The team will include a brief description of findings from previous related studies and justification in sufficient detail for the enrollment of children into the study.

6.2. A discussion that would support an IRB/EC assessment that the risks to participants are reasonable in relation to the anticipated benefits (if any) to participants, and the importance of the knowledge that may reasonably be expected to result;

6.2.1 Considerations for risk/benefit in sufficient details for the IRB/EC to determine into which of the four categories the research activity falls (see Appendix 1)

6.2.2 Classifying a particular activity into one of these categories involves, among other things, determining whether the proposed research involves "minimal risk" to the participants. The Subpart D regulations rely on the definition of "minimal risk" provided in Subpart A of the regulations.

6.2.3 Determining that a research activity presents no more than minimal risk involves comparing the possible harms or discomforts experienced in normal daily life or during routine physical or psychological examinations or tests with the possible harms or discomforts that will be faced by participants as a consequence of research participation. The nature of the harms or discomforts (e.g., physical, psychological, legal) should be considered, as well as the chances that they will occur and the seriousness of their impact if they were to happen. Including measures to prevent or decrease the likelihood of harm or discomfort from the research may affect

whether the proposed research activity involves no more than minimal risk. (See OHRP *FAQs on Research with Children.)*

6.3. When the child reaches legal age of consent

A description of the plan, where appropriate, for continuation of research participation when the child reaches legal age of consent;

If a study involves children who may r/each the legal age of consent during their participation in the research, the Protocol Team will identify whether there is a need to obtain the legally effective informed consent for the now-adult subject. This may be appropriate, for example, when the research involves ongoing interactions or interventions with the participants after they have reached the legal age of consent. Also, when a child who was enrolled in research with parental or guardian permission subsequently reaches the legal age of consent to the procedures involved in ongoing research, the participant's participation in the research is no longer regulated by the requirements of Subpart D regarding parental or guardian permission and subject assent. (See OHRP *FAQs on Research with Children* and DAIDS *Policy for Enrolling Children (including Adolescents) in DAIDS-Funded and/or Sponsored Human Subject Clinical Research: Clinical Research Site Requirements*.)

6.4. A description of the plan for obtaining informed consent from other individuals in addition to enrolled children, such as parents or family members who are human subjects in the research;

When family members of children enrolled in the research are asked to provide identifiable private information about themselves for research purposes, these individuals are considered human subjects in the research and they must also give their informed consent unless the IRB/EC finds and documents the criteria for waiver of informed consent to be met.

6.5. A description of the legal status of children without parents or who are not in the custody of their parents in the jurisdiction of the research, and plans for determining who can serve as a legal guardian in that jurisdiction for the purpose of providing permission for research participation;

6.6. Any additional conditions for certain research activities involving children who are wards of the State or any other agency, institution, or entity (see Appendix 3)

For research in categories 45 CFR 46.406, 21 CFR 50.53, 45 CFR 46.407, and 21 CFR 50.54, additional requirements must be met when research involves wards. For research approved under categories 45 CFR 46.404, 21 CFR 50.51, 45 CFR 46.405, and 21 CFR 50.52, there are no additional requirements when the research involves wards as participants (see Appendix 3).

6.7. Recommendations for obtaining parental or guardian permission

The Protocol Team will make recommendations for obtaining parental or guardian permission based upon the regulations at 45 CFR 46.408 and 21 CFR 50.55 and in accordance with written IRB/EC approved policies. (See Appendix 1 and DAIDS *Policy for Enrolling Children (including Adolescents) in DAIDS-Funded and/or Sponsored Human Subject Clinical Research: Clinical Research Site Requirements.)*

6.8 Waiver of parental/guardian permission

If a waiver of parental/guardian permission is to be requested in accordance with the provisions at 45 CFR 46.116(c) or 46.116(d), the Protocol Team should make every effort to provide sufficient detail in the protocol to justify the waiver. In accordance with the regulations, the IRB/EC must find and document that the criteria for the waiver are met.

NOTE: The provisions for waiver of parental/guardian permission in U.S. Food and Drug Administration (FDA) regulated clinical investigations are limited to 21 CFR 50.23, *Exception from General Requirements* and 21 CFR 50.24, *Exception from Informed Consent Requirements for Emergency Research.*

When the research is not FDA-regulated and does not meet the requirement for the waiver under 45 CFR 46.116(c) or 46.116(d), the IRB/EC may waive the requirements for obtaining parental/guardian permission if it determines that the research protocol is designed for a condition or for a subject population for which parental/guardian permission is not a reasonable requirement, to protect participants provided an appropriate mechanism for protecting the children who will participate in the research is substituted. In addition, the waiver must be consistent with Federal, State or local law (see 45 CFR 46.408(c)).

The conditions under which parental permission may be waived and examples of substitute protection mechanisms can be found in Appendix 2.

An example of when waiver of parental/guardian permission may be appropriate would be the conduct of a non-FDA regulated study of abused children.

6.9 Waiver of documentation of parental/guardian permission

If the Protocol Team seeks to waive documentation of parental/guardian permission, they must include sufficient details in the protocol documents for the IRB/EC to make the findings for approval of the waiver.

In accordance with 45 CFR 46.117(c)(2) and 21 CFR 56.109(c) the IRB/EC may waive the requirements for documentation of parental/guardian permission for research that presents no more than minimal risk of harm to participants and involves no procedure for which written consent is normally required outside of the research context. However, the IRB/EC may require the PI to provide parents/guardians with a written statement regarding the research.

In addition, for non-FDA regulated clinical investigations, if the only record linking the child and the research would be the assent document and the principal risk would be potential harm resulting from a breach in confidentiality, then the documentation of parental/guardian permission can be waived. Each parent/guardian will be asked whether they want documentation linking the child with the research and the parent/guardian's wishes will govern. However, the IRB/EC may require the PI to provide parents/guardians with a written statement regarding the research. See 45 CFR 46.117(c)(1)

NOTE: Studies that are subject to FDA regulation are not eligible for a waiver of documentation of parental/guardian permission unless they meet the criteria at 21 CFR 50.27 or 21 CFR 56.109(c).

6.10 Child Assent

6.8.1 The protocol document will include a statement as to whether eligible children could be capable of providing assent and if so, indicate that the IRB/EC-approved process for obtaining and documenting the child's assent will be followed. Local laws regarding the age to give consent, circumstances under which children may act as adults and identification of responsible persons for orphan children vary from place to place. The IRB/EC-

approved process will take into account the age, maturity, and psychological state of the children involved in the research (see DAIDS *Policy for Enrolling Children (including Adolescents) in DAIDS-Funded and/or Sponsored Human Subject Clinical Research: Clinical Research Site Requirements*).

These provisions may be made for all children involved in the research or for each child as deemed appropriate by the IRB/EC. A study that may enroll children over a wide age range is an example of a study that may have different assent requirements.

6.7.1 For eligible children who are adolescents, the assent requirements would more closely resemble that of an adult consent process.

6.7.2 Where children are less mature or of an age that limits their ability to understand, the process would involve more description of what the actual experience of participation in research is likely to be, how long it will take, or whether it might involve any pain or discomfort.

6.11 Waiver of Child Assent

The Protocol Team may request a waiver of assent from the IRB/EC if one of the three following circumstances is met (see Appendix 2):

1) the capability of some or all of the children is so limited that they cannot reasonably be consulted;

2) the intervention or procedure involved holds out the prospect of direct benefit to the health or well-being of the child and is only available in the research (they may document this determination and submit it to the IRB/EC for approval);

3) the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at either 45 CFR 46.116(c) or 45 CFR 46.116(d).

6.12 Research that is otherwise exempt from IRB/EC review:

The Protocol Team must take into account that some research activities that would be exempt if the research participants were adults requires IRB/EC review if the research activities involve children (45 CFR 46.101(b) and 21 CFR 56.104).

Examples of research **not** exempt from IRB/EC review when conducted in children include:

- surveys;
- interviews; and
- research involving public observation when the PI participates in the activities being observed.

7.0 REFERENCES

Code of Federal Regulations, Title 45, Part 46 Protection of Human Subjects
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

Code of Federal Regulations, Title 45, 46 Subpart D, Additional Protections for Children Involved as Subjects in Research
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

Code of Federal Regulations, Title 21, Part 50 Protection of Human Subjects
http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfr50_06.html

Code of Federal Regulations, Title 21, Part 50 Subpart D, Additional Safeguards for Children in Clinical Investigations
http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfr50_06.html

21 CFR 56, Institutional Review Boards
http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfr56_06.html

Office for Human Research Protections (OHRP) *FAQs on Research with Children*
http://www.hhs.gov/ohrp/policy/index.html#children

Federal Register: April 24, 2001 (Volume 66, Number 79) Additional Safeguards for Children in Clinical Investigations of FDA-regulated Products
http://www.fda.gov/OHRMS/DOCKETS/98fr/042401a.pdf

DAIDS *Policy for Enrolling Children (including Adolescents) in DAIDS-Funded and/or Sponsored Human Subject Clinical Research: Clinical Research Site Requirements*

8.0 INQUIRIES

Questions and comments regarding this policy may be directed to the OPCRO Policy Group at: NIAIDOPCROPOLICYGROUP@mail.nih.gov

9.0 AVAILABILITY

This policy is available electronically at the following URL:
http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Default.htm

10.0 CHANGE SUMMARY

This policy is the first version. It does not supersede any other version.

11.0 APPENDICIES

- Appendix 1 Risk/Benefit Categories
- Appendix 2 Waivers of Parental/Guardian Permission or Child Assent
- Appendix 3 Wards
- Appendix 4 Examples of Templated Language

12.0 APPROVAL

/Dr. Richard Hafner, MD/
Richard Hafner