DAIDS
Bethesda, MD USA

POLICY

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

Approval Date: Pending No.: DRAFT

1.0 PURPOSE

The purpose of this policy is to identify written policies and procedures required at all DAIDS sponsored clinical research sites enrolling children in research so as to ensure that enrollment is conducted in accordance with applicable U.S. Federal and State regulations and local laws and regulations. Local laws and regulations include those laws applicable in the country or jurisdiction where the research is conducted.

2.0 SCOPE

This policy applies to all clinical research sites sponsored by DAIDS or participating in DAIDS funded and/or sponsored human subject clinical research that intend 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. 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 (45 CFR 46 Subpart D). Local laws, regulations and customs regarding the age to give consent, circumstances under which children may act as adults and identification of responsible persons for children with out parents vary from place to place. Further, most clinical research involving drugs, devices, and biologics are also subject to U.S. Food and Drug Administration (FDA) regulations.

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 Institutional Review Boards (IRBs)/Research Ethics Committees (RECs) 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 required site policies and procedures. A companion policy, *Policy for Enrolling Children (including Adolescents) in DAIDS-Funded and/or Sponsored Human Subject Clinical Research: Protocol Document Requirements* describes protocol document content requirements and the responsibilities of the Protocol Team, the IRB/REC, and the Principal Investigator (PI).

4.0 DEFINITIONS

See DAIDS glossary.

5.0 RESPONSIBILITES

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/REC) with the research, the investigator(s), or the guardian organization. 45 CFR 46.409(b) The advocate is in addition to any other individual acting on behalf of the child as guardian or in loco parentis. 21 CFR 50.56(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: Research that involves an experimental drug or device and human subjects. Go to definition 21 CFR 50.3, 21 CFR 312.3, full 21 CFR 312, and full CFR 812. Also go to NIAID's Human Subjects, Clinical Research.

Clinical Research: Human subjects term indicating Research conducted on human subjects or material of human origin that can be personally identified. Policy covers large and small-scale, exploratory, and observational studies. There are three types:

1. Patient-oriented research.
2. Epidemiologic and behavioral studies.
3. Outcomes and health services research.

Clinical Trial: Human subjects term indicating a prospective study of human subjects designed to answer questions about biomedical or behavioral interventions, e.g., drugs, treatments, or devices or new ways of using known treatments to determine whether they are safe and effective.

1. Phase I tests a new intervention in 20 to 80 people for an initial evaluation of safety, e.g., to determine a safe dosage range and identify side effects.

2. Phase II studies an intervention in a larger group of people, usually several hundred, to determine efficacy and further evaluate safety.

3. Phase III studies the efficacy of an intervention in large groups of several hundred to several thousand subjects by comparing it to other standard or experimental interventions, while monitoring adverse events and collecting information that will allow safe use.

4. NIH-defined phase III clinical trial is a broad-based, prospective study, including community and other population-based trials, usually involving several hundred or more people, to compare an experimental intervention with a standard or control or compare existing treatments. It often aims to provide evidence for changing policy or standard of care. It includes pharmacologic, non-pharmacologic, and behavioral interventions for disease prevention, prophylaxis, diagnosis, or therapy.

5. Phase IV is a study done after an intervention has been marketed to monitor its effectiveness in the general population and collect information about adverse effects associated with widespread use.

Clinical Research Site: Discrete locations (e.g., hospitals, outpatient clinics, health maintenance organizations, community health centers, private practices, clinics) sponsored by DAIDS where qualified professionals conduct clinical research in accordance with Good Clinical Practices. (DAIDS)

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)

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)

For clinical trials conducted under FDA regulations, a guardian is 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. A guardian is also and individual who is authorized to consent on behalf of a child to participate 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) 21 CFR 50.3(k)

Parent: The child's biological or adoptive parent. 45 CFR part 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)

6.0 POLICY

6.1 Required Procedures. Clinical research sites planning or conducting DAIDS-funded and/or sponsored human subject clinical research that enrolls children, including adolescents, are required to develop, maintain, and adhere to written policies and procedures that:

6.1.1 direct site activities related to IRB/REC review and approval of research involving children;

6.1.2 direct activities related to the identification and enrollment of children; and

6.1.3 identify appropriate procedures for obtaining and documenting parental/guardian permission and child assent.

In some cases, clinical research sites with a predominantly adult clinical research focus will appropriately seek to enroll adolescents for whom the research is scientifically relevant and ethically appropriate; the specific criteria for enrollment of adolescents would be specified in the protocol. These sites are encouraged to also develop and maintain such written policies and procedures to expedite enrollment of eligible adolescents into adult-oriented clinical research.

6.2 The clinical research site's written policies and procedures for enrollment of children may be an institutional policy and procedure, IRB/REC policy and procedure, clinical research site policy and procedure, or a combination of the above. Policies and procedures developed at the clinical research site level must be submitted to the IRB/REC for review and written approval.

6.3 All clinical research site policies and procedures must be consistent with the requirements of 45 CFR 46 and any other applicable U.S. Federal, State, or local laws; National Institutes of Health (NIH), National Institute for Allergy and Infections Diseases (NIAID), or DAIDS policy.

6.4 ;Circumstances of a specific clinical research project may require the development of unique policies and procedures for the enrollment of children that are in addition to or supersede standard institutional, IRB/REC, or clinical research site policies and procedures. These policies must be consistent with 45 CFR 46 and FDA regulated research under 21 CFR Parts 50 and 56 as well as any other applicable U.S. Federal, State, or local laws.

6.5 IRB/REC Risk/Benefit Assessment. U.S. Federal regulations (45 CFR 46 Subpart D, and 21 CFR 50 Subpart D) require IRB/RECs to determine whether a proposed study involving children is more than minimal risk; whether there is a potential for direct benefit to participants; and, for studies considered to be greater than minimal risk, whether the study is likely to generate generalizeable knowledge. The outcome of these determinations place the research into one of the four categories identified below, each of which has important implications for study approval and need for additional protections.

45 CFR 46.404: Research not involving greater than minimal risk

21 CFR 50.51: Clinical investigations not involving greater than minimal risk

45 CFR 46.405: Research involving greater than minimal risk but presenting the prospects of direct benefit to individual subjects.

21 CFR 50.52: Clinical investigations involving greater than minimal risk but presenting the prospects of direct benefit to individual subjects.

45 CFR 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 subjects' disorder or condition.

21 CFR 50.53: Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subjects' disorder or condition.

45 CFR 46.407: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem

affecting the health or welfare of children. (This category requires a special level of Department of Health and Human Services (DHHS) review beyond that provided by the IRB/REC.)

21 CFR 50.54: Clinical investigations not otherwise approvable which present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (This category requires a special level of FDA review beyond that provided by the IRB/REC.)

Therefore, all DAIDS-sponsored clinical research sites enrolling children in clinical research must have procedures in place to ensure that:

6.5.1 designated clinical research site personnel and the PI are informed in writing of the results of the IRB/REC deliberations.

6.5.2 written determination of risk/benefit category as described in 6.5 above is maintained in the clinical research site essential documents file.

6.5.3 protections required by the IRB/REC assessment and decisions are implemented.

6.5.4 documentation of the IRB/REC decisions is forwarded to the Protocol Registration Office at DAIDS at the time of initial study registration, annual review, and review of amendments and letters of amendment. DAIDS requires submission of the documentation of the IRB/REC designation of a risk/benefit category from 45 CFR 46.404-407, (21 CFR50.51-54) and IRB/REC approval for involvement of children based on the determinations specified in that category. The documentation may be in the IRB/REC approval letter or in other official correspondence from the IRB/REC to the PI.

6.6 Parent or Guardian Permission. Policies and procedures must include a description of local standards identifying who may provide permission for general medical care or health care and, if applicable, consent to participate in research, and describe procedures to determine and document the appropriate individual(s) to provide permission. These policies and procedures must specifically incorporate the following information and the source of the information (local laws):

6.6.1 The local legal standards for guardianship, as authorized under applicable State or local law, in the event of the inability of one or both parents to provide care and permission due to death, being unknown, not readily available, or not competent. This should include a description of the circumstances under which family and non-family members assume guardianship, or legal actions required to obtain guardianship, and required documentation, if any.

6.6.2 In these situations, to ensure regulatory compliance, an affirmative statement that the proposed consent process is authorized under applicable law must be sought from the official or agency with the authority to provide a definitive interpretation of the laws in the jurisdiction where the research is being conducted.

6.7 Other Circumstances. Under some circumstances, individuals who would not normally be able to give their consent may provide their own consent, depending on the jurisdiction of the research. For example, in some states, adolescents who consent to their own medical care in certain settings may not be considered children under 45 CFR 46 Subpart D. These policies and procedures must specifically incorporate the following information and the source of the information (local laws):

6.7.1 The legal age for consent to treatments or procedures involved in clinical research, under the applicable law of the jurisdiction in which the research will be conducted.

6.7.2 The legal age for consent to participate in research if the jurisdiction in which the research will be conducted has such laws or regulations.

6.7.3 Age and circumstances (such as marriage and pregnancy) under which individuals are permitted to act independently.

6.8 Waiver of parental/guardian permission. Under some circumstances (stated in 45 CFR 46.408(c)), the requirements for obtaining parental/guardian permission may be waived by the IRB/REC if the IRB/REC determines that the research protocol is designed for conditions or for a subject population for which parental/guardian permission is not a reasonable requirement to protect subjects (for example, neglected or abused children) provided an appropriate mechanism for protecting the children who will participate in the research is substituted. The waiver must be consistent with Federal, State, or local law.

NOTE: The provisions for waiver of parental/guardian permission in 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.*

6.9 Waiver of documentation of parental/guardian permission. Under some specific circumstances (stated in 45 CFR 46.117(c)), the IRB/REC may waive the requirement for the documentation of parental/guardian permission. Clinical research sites may anticipate the need to request such waivers for individual children or groups of children and develop written procedures based on IRB/REC requirements and applicable laws and regulations.

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 Assent Procedures. All DAIDS-sponsored clinical research sites planning to enroll children in clinical research must have a written policy for the assent of children that is in compliance with U.S. Federal regulations (45 CFR 46 Subpart D, 21 CFR 50 Subpart D) and any applicable Federal, State, and local laws and regulations. Determining whether eligible children are likely to be capable of providing assent based on the age, maturity, and psychological state is a responsibility of the IRB/REC. At the time of IRB/REC review, the IRB/REC may determine that all, some, or none of the children may be able to provide assent. The clinical research site must have written procedures for determining and documenting whether individual children are capable of providing assent, the content and procedure for assent, and that such assent was obtained.

6.11 Durability of Consent or Permission. Clinical research sites must have written procedures for each protocol to ensure that legally effective consent is maintained and to determine when re-consent should be sought. For example, the IRB/REC may require that re-consent be sought when there is a change in the person(s) who serves as guardian or when a participant reaches legal age of consent or is emancipated for other reasons. There must be procedures in place to ensure that the authorized person provides permission in cases where the IRB/REC requires re-consent of participants or parental permission.

In addition, there should be written policies in place that address studies involving children who may reach the legal age of consent during their participation in the research. The policy will describe whether a new consent process will be conducted with the now-adult participant, for example, in cases where there are ongoing interactions or interventions with the participants. Also, when a child who was enrolled in research with parental or guardian permission subsequently reaches the legal age to 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 participant assent. (See OHRP *FAQs on Research with Children* and DAIDS *Policy for Enrolling Children (including Adolescents) in DAIDS-Funded and/or Sponsored Human Subject Research: Protocol Document Requirements.)*

6.12 Protections for Wards. Subpart D mandates additional protections for children who are wards of the State or any other agency, institution, or entity. Such children can be enrolled in clinical research approved under sections 45 CFR 46.406, 21 CFR 50.53, or 45 CFR 46.407, 21 CFR 50.54 only if the research is either a) related to their status as wards or b) conducted at a location in which most of the children enrolled as subjects are not wards.

6.12.1 Clinical research sites enrolling children into DAIDS-funded and/or sponsored clinical research meeting category 45 CFR 46.406 or 46.407 and 21 CFR 50.53 or 50.54 must have written procedures to facilitate and document the recognition of the status of an individual child as a ward and ensure communication of that status to the responsible IRB/REC.

6.12.2 The designated IRB/REC must have written policies and procedures consistent with 45 CFR 46.409 and 21 CFR 50.56 to determine the requirement for and appointment of an advocate. These requirements must include that:

6.12.2.1 An advocate must be an individual who has the background and experience to act in, and agrees to act in, and represent the best interests of the child for the duration of the child's participation in the research. (An individual may serve as advocate for more than one child.)

6.12.2.2 The advocate must not be associated in any way (except in the role as advocate or member of the IRB/REC) with the research, the investigator(s), or the guardian organization.

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

Draft Guidance for Clinical Investigators, Institutional Review Boards, and Sponsors: Process for Handling Referrals to the FDA: Additional Safeguards for Children in clinical Investigations
http://www.fda.gov/OHRMS/DOCKETS/98fr/06d-0172-gdl0001.pdf

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

Children Involved as Subjects in Research: Guidance on the HHS 45 CFR 46.407 ("407") Review Process. May 26, 2005 Guidance
http://www.hhs.gov/ohrp/children/guidance_407process.html

DAIDS *Policy for Enrolling Children (including Adolescents) in DAIDS-Funded and/or Sponsored Human Subject Clinical Research: Protocol Document 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 on the DAIDS "Clinical Trial Planning and Implementation" website and on the DAIDS ES portal. The signed and dated original is maintained in the OPCRO policy office.

10.0 CHANGE SUMMARY

This policy supersedes DAIDS OPCRO Memorandum, *Required Documentation of Risk/Benefit Category and Approval of Clinical Studies for Inclusion of Children by IRBs/RECs based on 45 CFR 46, Subpart D*, dated July 8, 2005.

11.0 APPENDICIES

None

12.0 APPROVAL

/Dr. Richard Hafner, MD/
Richard Hafner