

ARCHIVED POLICY

Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site
Requirements

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1.0 PURPOSE

The purpose of this policy is to identify written policies and procedures required at all National Institute of Allergy and Infectious Disease (NIAID) Division of AIDS (DAIDS) -supported and/or -sponsored clinical research sites enrolling children in research so as to ensure that research with children 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 NIAID (DAIDS) or participating in NIAID (DAIDS) -supported and/or -sponsored clinical research that intend to enroll children (including adolescents) in clinical research.

3.0 BACKGROUND

NIAID (DAIDS)-supported and/or -sponsored 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 and, when applicable, the U.S. Food and Drug Administration (FDA) regulations, including 21 CFR 50, 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 without parents vary from place to place.

A significant portion of NIAID (DAIDS)-supported and/or -sponsored 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 (ECs) at diverse institutions. In order to ensure that NIAID (DAIDS)-supported and/or -sponsored 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, Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements describes protocol document content requirements and the responsibilities of the Protocol Team, IRB/EC, Clinical Research Site leader (CRS Leader), and Principal Investigator (PI).

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. The advocate is in addition to any other individual acting on behalf of the child as guardian or in loco parentis.¹

Assent: A child's affirmative agreement to participate in research. Mere failure to object should not, absent of affirmative agreement, be construed as assent.²

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.³

Clinical investigation: Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA or the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. FDA has defined "clinical investigation" to be synonymous with "research".⁴

Clinical investigator: A qualified professional that conducts clinical research activities including: collaboration and information exchange with community representatives; recruitment; enrollment; protocol visit conduct; management of study products; assessment and reporting of critical events; collection and management of clinical research data; communication of data; and creation, maintenance and storage of research records including participant files, source documents, regulatory files, subject identification information, clinical reports, and case report forms. (DAIDS)

Clinical research: 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.

¹ 45 CFR §46.409(b) & 21 CFR §50.56(b)

² 45 CFR §46.402(b) & 21 CFR §50.3(n)

³ 45 CFR §46.402(a) & 21 CFR §50.3(o)

⁴ <http://www.fda.gov/oc/gcP/comParison.html>

3. Outcomes and health services research. (DAIDS)

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

Clinical research site (CRS) leader: The onsite senior research scientist responsible for the administrative and scientific components of the CRS. The CRS leader is responsible for overall site activities, including day-to-day operations, performance, and compliance at the site level. (DAIDS)

Clinical trial: 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. (NIAID)

DAIDS supported: Human subjects research activities would be considered to be supported by NIAID (DAIDS) under any one of the following circumstances:

- (1) NIAID (DAIDS) provides direct funding to an institution via a grant, contract or cooperative agreement for the human subjects research activities; or (b) indirect funding via a subcontract executed under a NIAID (DAIDS) supported award to another institution; or
- (2) NIAID (DAIDS) provides other tangible support for the human subject research activities which includes, but is not limited to, regulatory support, site monitoring services, study product supply, management and distribution services; or
- (3) NIAID (DAIDS) -supported central laboratory or data management center receives from other organization specimens or data for processing or analysis and the results or analyses will be used to direct involvement of some or all subjects in the conduct of the clinical research activities. (DAIDS)

DAIDS sponsored: NIAID (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)

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.⁵

Guardian: An individual who is authorized to consent on behalf of a child to general medical care under applicable local law where the research is being conducted.⁶

For clinical trials conducted under FDA regulations, a guardian is an individual who is authorized to consent on behalf of a child to general medical care when general medical care includes participation in research under the applicable local law where the research is being conducted. A guardian is also an individual who is authorized to consent on behalf of a child to participate in research.⁷

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.⁸

Parent: The child's biological or adoptive parent.⁹

Permission: The agreement of parent(s) or guardian to the participation of their child or ward in research.¹⁰

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. (NIH)

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives

⁵ 21 CFR §50.3(m)

⁶ 45 CFR §46.402(e)

⁷ 21 CFR §50.3(s)

⁸ 45 CFR §46.102(i) & 21 CFR §50.3(k)

⁹ 45 CFR §46.402(d) & 21 CFR §50.3(p)

¹⁰ 45 CFR §46.402(c) & 21 CFR §50.3(r)

the background and rationale for the trial, but these could be provided in other protocol referenced documents.¹¹

Protocol team: A team of individuals comprised of grantees, investigators, statisticians, and other protocol support personnel who work to develop concepts into NIAID (DAIDS)-supported 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.¹²

For additional definitions see DAIDS Glossary:

<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Glossary>

5.0 RESPONSIBILITIES

Protocol Team

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.

IRB/EC

An *IRB/EC* identified on the Federalwide Assurance of the institution that is engaged in the research is responsible for the review of all clinical research enrolling children, and determining that all of the regulatory requirements are satisfied, including that risks to the child-participants are reasonable in relationship to anticipated benefits¹³ and that there are adequate provisions for soliciting the assent of the child and permission of child-participants' parents or guardians¹⁴. The *IRB/EC* is responsible for determining when each child or all children are capable of

¹¹ ICH E6 1.44

¹² 21 CFR §50.3(q)

¹³ 45 CFR §46.111 and Subpart D; 21 CFR 50, subpart D, 21 CFR §56.109; 21 CFR §56.111(2)

¹⁴ 45 CFR §46.408 and 21 CFR §50.55

assent, whether and how assent must be documented, and when assent is not necessary or can be waived¹⁵.

CRS Leader

The *CRS Leader* 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.

Principal Investigator

The *Principal Investigator* is 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. The Principal Investigator is also responsible for the following activities:

Conducting the clinical research in accordance with the requirements or determinations of the IRB/EC;

Obtaining and documenting parental/guardian permission and child assent prior to the child's participation in the research, unless these requirements have been waived by the IRB/EC;

Obtaining prior approval from the IRB/EC for any modifications of the previously approved research, including modifications to the parental/guardian permission and child assent process and document, except those necessary to eliminate apparent immediate hazards to the child-subjects;

Ensuring that progress reports and requests for continuing review and approval are submitted to the IRB/EC in accordance with the policies, procedures, and actions of the IRB/EC;

Prompt reporting to the IRB/EC of any unanticipated problems involving risks to subjects or others;

¹⁵ 45 CFR §46.408 21 CFR §50.55

Prompt reporting to the IRB/EC of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB;

Keeping certain records as required by the HHS and FDA regulations for at least three years after completion of the study.

Clinical Investigator

Clinical investigators are responsible for conducting the clinical research in accordance with the requirements or determinations of the IRB/EC.

6.0 POLICY

6.1 Required Policies and Procedures

Clinical research sites planning or conducting clinical research with children, including adolescents, are required to develop, maintain, and adhere to written policies and procedures that:

- 6.1.2 direct site activities related to IRB/EC review and approval of research involving children;
- 6.1.3 direct activities related to the identification and enrollment of children; and
- 6.1.4 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/EC 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/EC 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), 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/EC, or clinical research site policies and procedures. These policies must be consistent with 45 CFR 46 and, for FDA regulated research, with 21 CFR Parts 50 and 56 as well as any other applicable U.S. Federal, State, or local laws.
- 6.5 IRB/EC Risk/Benefit Assessment

U.S. Federal regulations¹⁶ require IRB/ECs 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 generalizable knowledge. The outcome of these determinations places the research into one of the four regulatory categories identified below, each of which has important implications for study approval and need for additional protections.

6.5.1 45 CFR §46.404: Research not involving greater than minimal risk

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

6.5.2 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.

¹⁶ 45 CFR 46, subpart D & 21 CFR 50, subpart D

6.5.3 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.

6.5.4 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/EC.)

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/EC.)

Therefore, all clinical research sites conducting clinical research with children must have procedures in place to ensure that:

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

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

6.5.7 protections required by the IRB/EC assessment and decisions are implemented.

6.5.8 documentation of the IRB/EC 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/EC designation of a risk/benefit category from 45 CFR §§46.404-407 or 21 CFR §§50.51-54, and IRB/EC approval for involvement of children based on the determinations specified in that

category. The documentation may be in the IRB/EC approval letter or in other official correspondence from the IRB/EC to the PI.

6.6 Guardian Permission

Clinical research sites conducting clinical research with children may wish to include children for whom one or both parents are unable to provide permission due to the parent(s) being dead, unknown, not readily available, or not competent. In these circumstances, federal regulations allow a guardian to provide permission for the child to participate or continue participation in the research.

In anticipation of such circumstances, clinical research sites planning or conducting clinical research with children must have written procedures describing the local standards identifying who may serve as *guardian*¹⁷.

6.6.1 In countries where the local legal standards for guardianship exist

In countries where the local legal standards for guardianship are *clearly defined*, the clinical research site procedures will include a description of the circumstances under which family and non-family members assume guardianship, as authorized under local law or legal actions required to obtain guardianship, and required documentation, if any.

In countries where the local legal standards for guardianship are *vague*, the clinical research site procedures will include an explanation of the process to identify a guardian. The sponsor or its designee will obtain a definitive interpretation of the applicable law respecting the identification and appointment of a guardian in the jurisdiction where the research will be conducted from an authorized government official or agency.

6.6.2 In countries where the local legal standards for guardianship do not exist

In countries where the local legal standards for guardianship are *absent*, the clinical research site procedures will include an explanation of the process to identify a guardian. The sponsor or its designee will obtain an affirmative statement from a governmental official or

¹⁷ 45 CFR 46.402(e) and 21 CFR 50.3(s)

agency with the authority to approve a customary process for identifying and appointing a guardian in the jurisdiction where the research will be conducted.

6.6.3 Other considerations related to guardian permission

Written procedures may also include:

- 6.6.3.1 What documentation will be required for recognition of such guardianship, if any;
- 6.6.3.2 How guardianship disputes will be handled for purposes of a child's participation in research.

The site's procedures for recognizing guardianship should be based on applicable local law, regulation, or government policy, where available. Development of the site's written procedures may require consultation with relevant government authorities to ensure accuracy and clarity in the interpretation and application of these guardianship standards.

In all cases, the written procedures for recognizing guardianship should document the source of information or authority relied upon, and justify the reasonableness of such reliance (e.g., why an informal government policy is the most appropriate standard for recognizing guardianship in this context, or how local custom was validated and assessed). The procedures should be updated as needed to reflect potential changes in applicable legal standards.

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 are not considered children under 45 CFR 46, subpart D. The site's 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, the HHS regulations allow the IRB/EC to waive the requirement to obtain parental/guardian permission. In addition to the provisions for waiver under Subpart A¹⁸, if the IRB/EC 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 subjects¹⁹ (for example, neglected or abused children), the IRB/EC may the waive the requirement to obtain parental/guardian permission, provided an appropriate mechanism for protecting the child- participants is substituted. The waiver must be consistent with Federal, State, or local law. Clinical research sites may anticipate the need to request waiver of parental/guardian permission for individual children or groups of children and develop written procedures based on IRB/EC requirements and applicable laws and regulations.

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, the HHS regulations²⁰ allow the IRB/EC to waive the requirement to obtain a signed parental/guardian permission form. Clinical research sites may anticipate the need to request waiver of documentation of parental/guardian permission for some or all

¹⁸ 45 CFR §46.116(c) & (d)

¹⁹ 45 CFR §46.408(c)

²⁰ 45 CFR §46.117(c)

child-participants and develop written procedures based on IRB/EC 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 NIAID (DAIDS)-supported and/or -sponsored clinical research sites planning to enroll children in clinical research must have a written policy and procedure for the assent of children that is in compliance with applicable U.S. Federal regulations²¹ and any other 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/EC. At the time of IRB/EC review, the IRB/EC may determine that all, some, or none of the children may be able to provide assent. The clinical research site's written procedure for assent must include the process that will be followed for determining and documenting whether individual children are capable of providing assent, the content and procedure for assent, and that such assent was obtained, based on the IRB/EC's determinations for obtaining assent.

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/EC 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/EC requires re-consent of participants or parental permission.

6.11.1 Children who reach the legal age of consent

Clinical research sites should have a written policy that addresses the actions to take when children reach the legal age of consent during their participation in the research. The policy should describe whether a new consent process

²¹ 45 CFR 46, subpart D and 21 CFR 50, subpart D

will be conducted with the now-adult participant, for example, in cases where there are ongoing interactions or interventions with the participants. Note that 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 now-adult'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 Clinical 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 and 21 CFR §50.53, or 45 CFR §46.407 and 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 To enroll children who are wards into NIAID (DAIDS)-supported and/or -sponsored clinical research that is approved under category 45 CFR §46.406 or §46.407 and 21 CFR §50.53 or §50.54, the site 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/EC.

6.12.2 The designated IRB/EC must have written policies and procedures consistent with the applicable regulations²² 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.)

²² 45 CFR §46.409 and 21 CFR §50.56

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

7.0 REFERENCES

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

Code of Federal Regulations, Title 45 CFR 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 CFR Part 50 Protection of Human Subjects
http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfr50_06.html

Code of Federal Regulations, Title 21 CFR 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

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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 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

None

12.0 APPROVAL

/Richard Hafner, MD/
Richard Hafner