

DAIDS
Bethesda, MD USA

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements

Approval Date: 05 OCT 2015

No.: DWD-POL-CL-08.02

Effective Date: 02 NOV 2015

CHANGE SUMMARY NOTE: This Policy has been reviewed for accuracy and updated to meet 508 compliance guidelines. This version supersedes version 1.0 dated 25 JUL 2009.

1.0 PURPOSE

The purpose of this policy is to describe the special contents required in protocols of National Institute of Allergy and Infectious Disease (NIAID) Division of AIDS (DAIDS)-supported and/or -sponsored 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 NIAID (DAIDS)-supported and/or -sponsored clinical research that intends 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. 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 IRBs/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 protocol document requirements. A companion policy, Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements, describes required written site policies and procedures and responsibilities of the Protocol Team, IRB/EC, Clinical Research Site (CRS) Leader, and the Principal Investigator (PI).

U.S. Regulatory Requirements

In addition to the regulatory requirements that list the Criteria for IRB Approval of Research (45 CFR 46.111 and 21 CFR 56.111), U.S. Federal regulations governing

DAIDS
Bethesda, MD USA

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements

Approval Date:

No.: DWD-POL-CL-08.02

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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 for additional information on risk/benefit categories).

4.0 DEFINITIONS

For definitions, see [DAIDS 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 benefits [45 CFR 46.111 and Subpart D; 21 CFR 50, subpart D, 21 CFR 56.109; 21 CFR 56.111(2)] and that there are adequate provisions for soliciting the assent of the child and permission of child-participants' parents or guardians [45 CFR 46.408 and 21 CFR 50.55]. The IRB/EC is responsible for determining when each child or all children are capable of

DAIDS
Bethesda, MD USA

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Protocol Document
Requirements

Approval Date:

No.: DWD-POL-CL-08.02

Effective Date:

assent, whether and how assent must be documented, and when assent is not necessary or can be waived [45 CFR 46.408 21 CFR 50.55].

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.

Principle 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.

6.0 POLICY

6.1 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 the protocol, the following information required for the IRB/EC to review and approve the protocol.

6.1.1 IRB/EC criteria that must be satisfied

6.1.1.1 A brief description of findings from previous related studies and justification in sufficient detail for the enrollment of children into the study.

6.1.1.2 A description of the research that would allow 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;

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Protocol Document
Requirements

Approval Date:

No.: DWD-POL-CL-08.02

Effective Date:

6.1.1.3 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 for details on risk/benefit categories and Appendix 2 for examples of risk category templated language)

6.1.1.3.1 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.

6.1.1.3.2 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.)

6.1.2 When the child reaches legal age of consent

Recommendations, where appropriate, for continuation of research participation when the child reaches legal age of consent.

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Protocol Document
Requirements

Approval Date:

No.: DWD-POL-CL-08.02

Effective Date:

If a study involves children who may reach 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. 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 involvement 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 Clinical Research: Clinical Research Site Requirements.)

6.1.3 Obtaining informed consent from other individuals involved in research

Recommendations 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.

6.1.4 Information when enrolling wards

Additional information to be provided to the IRB/EC for enrolling children in the research who are wards of the State or any other agency, institution, or entity under the following conditions:

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Protocol Document
Requirements

Approval Date:

No.: DWD-POL-CL-08.02

Effective Date:

6.1.4.1 when there are definite plans to enroll such participants for research; and

6.1.4.2 when the research will be approved by the IRB/EC under categories 45 CFR 46.406, 21 CFR 50.53, 45 CFR 46.407, and/or 21 CFR 50.54.

The information provided to the IRB/EC should include if the research is:

1. Related to the participants status as wards; or
2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(See Appendix 3 and DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements.)

6.1.5 Recommendations for obtaining parental or guardian permission

As appropriate, recommendations for obtaining parental or guardian permission based upon the regulations at 45 CFR 46.408 and 21 CFR 50.55 for review and approval by the IRB/EC.

(See Appendix 1 for details on parental permission requirements associated with each risk/benefit category, Appendix 2 for examples of templated language associated with parental/guardian permission choices, and DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements.)

6.1.6 Waiver of parental/guardian permission

If a waiver of parental/guardian permission is likely to be requested by the site investigators in accordance with the provisions at 45 CFR 46.116(c) or 46.116(d), provide sufficient detail to justify the waiver.

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Protocol Document
Requirements

Approval Date:

No.: DWD-POL-CL-08.02

Effective Date:

In accordance with the regulations, the IRB/EC must find and document that the criteria for the waiver are met. The conditions under which parental permission may be waived and examples of substitute protection mechanisms can be found in Appendix 4.

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)).

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.

6.1.7 Waiver of documentation of parental/guardian permission

If it is likely that the site investigator will request waiver of documentation of parental/guardian permission, provide sufficient details 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

DAIDS
Bethesda, MD USA

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Protocol Document
Requirements

Approval Date:

No.: DWD-POL-CL-08.02

Effective Date:

procedure for which written consent is normally required outside of the research context. However, the IRB/EC may require the site investigator 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 consent 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 site investigator to provide parents/guardians with a written statement regarding the research. See 45 CFR 46.117(c)(1) for further information on this type of waiver of documentation of parental/guardian permission.

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).

6.1.8 Child Assent

Include recommendations on whether eligible children could be capable of providing assent, include a plan for the process of obtaining assent in the protocol and indicate that the IRB/EC-approved process for obtaining and documenting the child's assent will be followed. (see DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements.)

The provisions to obtain child assent may be made for all children involved in the research or to address 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.

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Protocol Document
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Approval Date:

No.: DWD-POL-CL-08.02

Effective Date:

- 6.1.8.1 For eligible children who are adolescents, the assent requirements would more closely resemble that of an adult consent process.
- 6.1.8.2 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.

6.1.9 Waiver of Child Assent

If it is likely that a waiver of assent will be requested from the IRB/EC, sufficient details in the protocol for the IRB/EC to make the finding for approval of the waiver.

Assent may be waived by the IRB/EC if one of the three following circumstances is met:

- 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).

(See Appendix 2 for examples of templated language associated with child assent choices and Appendix 4 for regulations pertaining to waiving child assent.)

DAIDS
Bethesda, MD USA

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Protocol Document
Requirements

Approval Date:

No.: DWD-POL-CL-08.02

Effective Date:

6.2. 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:

1. surveys;
2. interviews; and
3. research involving public observation when the investigator(s) participates in the activities being observed.

7.0 REFERENCES

[Code of Federal Regulations, Title 45, Part 46 Protection of Human Subjects](#)

[Code of Federal Regulations, Title 45 CFR Part 46, subpart D, Additional](#)

[Code of Federal Regulations, Title 21 CFR Part 50 Protection of Human Subjects](#)

[21 CFR 56, Institutional Review Boards](#)

[Office for Human Research Protections \(OHRP\) FAQs on Research with Children](#)

[Federal Register: April 24, 2001 \(Volume 66, Number 79\) Additional Safeguards for Children in Clinical Investigations of FDA-regulated Products](#)

[DAIDS Policy for Enrolling Children \(including Adolescents\) in Clinical Research: Clinical Research Site Requirements](#)

8.0 INQUIRIES

Questions and comments regarding this SOP may be directed to the [OPCRO Policy Group](#).

DAIDS
Bethesda, MD USA

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Protocol Document
Requirements

Approval Date:

No.: DWD-POL-CL-08.02

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9.0 AVAILABILITY

This policy is available electronically on the [Division of AIDS \(DAIDS\) Clinical Research Policies and Standard Procedures](#) webpage.

10.0 APPENDICES

Appendix 1 Risk/Benefit Categories

Appendix 2 Examples of Template Language

Appendix 3 Wards

Appendix 4 Waivers of Parental/Guardian Permission or Child Assent

11.0 APPROVAL

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