Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual Appendix:

Clinical Research Site Requirements for Enrolling Minors into DAIDS Clinical Research

Clinical Research Sites (CRSs) enrolling minors must follow the requirements of this appendix when developing and implementing a Standard Operating Procedure (SOP) for enrolling minors into DAIDS clinical research. The CRS's SOP for enrollment of minors may be based on an Institutional policy, Institutional Review Board (IRB)/Ethics Committee (EC) requirements, CRS policies and procedures, or a combination of the above. CRSs must submit this SOP to the Office of Clinical Site Oversight (OCSO) Program Officer (PO) for review and approval prior to implementation.

The CRS processes for enrolling minors must comply with the requirements of:

- United States (U.S.) 45 Code of Federal Regulations (CFR) part 46;
- International Council for Harmonisation (ICH) Good Clinical Practices (GCP), also referred to as ICH E6;
- 21 CFR parts 50 and 56 (U.S. Food and Drug Administration (FDA)-regulated studies);
- Applicable federal and local laws;
- National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), and DAIDS.

The CRS SOP for enrolling minors must:

- Direct CRS activities related to IRB/EC review and approval of clinical research involving minors.
- Direct CRS activities related to identifying and enrolling minors.
- Identify appropriate procedures for obtaining and documenting assent from the potential minor participants.
- Identify appropriate procedures for obtaining and documenting consent from the parents or legal guardian.
- Identify procedures for assenting minors once they reach the age of assent.
- Identify procedures for obtaining consent once the minor participants reach the locally defined age of majority during the course of the study.
- Identify appropriate procedures detailing CRS obligations if the parent or legal guardian of a minor enrolled in any DAIDS clinical research dies.

- Directs the CRS to handle unique situations for enrollment of minors that may arise during a study.

If the CRSs with a predominantly adult clinical research focus will seek to enroll adolescents for whom the research is scientifically relevant and ethically appropriate, these CRSs should also develop and maintain written SOPs for the process of enrollment of eligible adolescents into adult oriented clinical research.

Institutional Review Board/Ethics Committee Risk Benefit Assessment

CRSs must provide to the IRB/EC all relevant clinical research documentation that will enable the IRB/EC to determine the level of risk to minors from participation in clinical research. U.S. Federal regulations (45 CFR part 46, subpart D and 21 CFR part 50, subpart D) require IRB/ECs to determine whether the proposed clinical research involving minors is more than a minimal risk; whether there is a potential for direct benefit to the minor 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 described below, each of which has important implications for clinical research approval and need for additional protections.

- 45 CFR part 46.404: Research not involving greater than minimal risk. 21 CFR part 50.51: Clinical investigations not involving greater than minimal risk.
- 45 CFR part 46.405: Research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. 21 CFR part 50.52: Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.
- 45 CFR part 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 part 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 part 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 part 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 CRSs conducting DAIDS clinical research with minors must have an SOP in place that describes CRS procedures to ensure that:

- Designated CRS personnel and the Principal Investigators (PIs)/Investigators of Record (IoRs) are informed in writing of the results of the IRB/EC deliberations.
- Written determination of the risk/benefit category from the IRB/EC is maintained in the essential documents file.
- Protections required by the IRB/EC assessment and decisions are implemented.

DAIDS Protocol Registration Office (PRO) Approval

The SOP should direct the CRS staff to submit the documentation of the IRB/EC decisions to the PRO at the time of initial study registration, annual review and review of amendments and letters of amendments per the DAIDS Protocol Registration Manual.

DAIDS requires submission of the documentation of the IRB/EC designation of a risk/benefit category from 45 CFR part 46.404-407 or 21 CFR part 50.51-54, and approval for involvement of minors based on the determinations specified in these categories. The approved category of clinical research may be documented in the IRB/EC approval letter or in other official correspondence from the IRB/EC to the PI/IoR.

Legal Guardian Permission

CRSs planning or conducting clinical research with minors must have written procedures describing the local standards identifying who may serve as legal guardian when both parents are unable to provide permission due to the parent(s) being dead, unknown, not readily available, or not competent (45 CFR part 46.402[e] and 21 CFR part 50.3[s]). In these circumstances, U.S. federal regulations allow the legal guardian to provide permission for the minor to participate or continue participation in the clinical research.

CRS staff obtaining informed consent will rely on the SOP's definition to determine whether an individual qualifies to consent as a legal guardian on behalf of a potential minor participant. The specificity of local laws varies; as such, CRSs must consider the following when defining legal guardian qualifications in this SOP.

- If the clinical research will be conducted in a country with clearly defined guardian ship laws, CRS procedures will describe the circumstances under which family or non-family members are authorized to assume legal guardian responsibilities, and the documentation required (if any) to be reviewed and kept in the participant´s research record as evidence of the legal guardian authorization.
- If the clinical research will be conducted in a country with vague guardian ship laws, CRS procedures will explain how CRSs ensure that someone who presents as a legal guardian is legally qualified. DAIDS or its designee will obtain a definitive interpretation of the applicable law respecting the identification and appointment of

a legal guardian in the jurisdiction where the study will be conducted from an authorized government official or agency.
- If the clinical research will be conducted in a country with no established guardian ship laws, CRS procedures will explain how they identify a legal guardian. For CRSs in such locations, the process/SOP must be reviewed by the IRB/EC.

Evidence of Legal Guardianship
The CRS SOP must list the documents that may serve as evidence that an individual is legally authorized to represent a potential minor participant and how CRSs should handle any guardianship disputes if they arise.

CRSs should use applicable, available local laws and regulations to define their procedures for recognizing legal guardians. Development of these procedures may require consultation with relevant local government authorities to ensure accuracy and clarity in the interpretation and application of guardianship standards. The SOP must also reference the source of this information or the government authority this information was received from or relied upon and justify the reasonableness of reliance on this information. CRSs should update procedures as needed to reflect any changes in applicable legal standards.

Other Circumstances

Under some circumstances, individuals who would normally be unable to consent may provide their own consent, depending on governing laws in the jurisdiction where the CRS is conducting a clinical research. For example, in some states, minors who consent to their own medical care in certain settings are not considered children under 45 CFR part 46, subpart D. The CRS's SOP must specifically incorporate the following information and cite source of this information (e.g., applicable local laws of the jurisdiction where the CRS will conduct the clinical research):

- Legal age that permits an individual to consent to clinical research–related treatments or procedures.
- Legal age that permits an individual to consent to participate in clinical research.
- Circumstances (such as marriage and pregnancy) and corresponding age at which minors are permitted to consent independently.

Waiver of Parental/Legal Guardian Permission

In U.S. for non-FDA regulated clinical research, the HHS regulations under some circumstances allow IRB/EC to waive the requirement to obtain parental/legal guardian permission. In addition to the provisions for waiver under Subpart A [45 CFR part 46.116(e) & (f)], if the IRB/EC determines that the clinical research is designed for conditions or for a participant population for which parental/legal guardian permission is not a reasonable requirement to protect participants [45 CFR part 46.408(c)] (for example,

neglected or abused children), the IRB/EC may the waive the requirement to obtain parental/legal guardian permission, provided an appropriate mechanism for protecting the minor participants is substituted. The waiver must be consistent with Federal, State, or local law. CRSs may anticipate the need to request waiver of parental/legal guardian permission for individual minors or groups of minors and develop written procedures based on IRB/EC requirements and applicable laws and regulations. The CRS's SOP must include how CRS staff will document consenting a minor participant if the IRB/EC waives the requirement to obtain the parental/legal guardian permission.

Note: The provisions for waiver of parental/legal guardian permission in FDA regulated clinical investigations are limited to 21 CFR part 50.23, Exception from General Requirements and 21 CFR part 50.24, Exception from Informed Consent Requirements for Emergency Research.

Waiver of Documentation of Parental/Legal Guardian Permission
In U.S. for non-FDA regulated clinical research, the HHS regulations [45 CFR part 46.117(c)] allow the IRB/EC to waive the requirement to obtain a signed parental/legal guardian permission form. CRSs may anticipate the need to request waiver of documentation of parental/legal guardian permission for some or all minor participants and develop written procedures based on IRB/EC requirements and applicable laws and regulations.

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

Assent Procedures

All DAIDS CRSs planning to enroll minors in clinical research must have a written procedure for the assent of minors that is in compliance with applicable U.S. Federal regulations [45 CFR 46, subpart D and 21 CFR 50, subpart D] and any other applicable Federal, State, and local laws and regulations. Determining whether eligible minors 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 minors may be able to provide assent. The CRS's written procedure for assent must include the process that will be followed for determining and documenting whether individual minors are capable of providing assent, the content and procedure for assent, and that such assent was obtained, based on the IRB's /EC's determinations for obtaining assent.

Durability of Consent or Permission

CRSs 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 parent/legal 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/legal guardian permission.

Minors Who Reach the Legal Age of Consent

CRSs should have a written procedure that address the actions to be taken when minors reach the legal age of consent during their participation in clinical research. The procedure should 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. Note that when a minor who was enrolled in clinical research with parental permission subsequently reaches the legal age to consent to the procedures involved in ongoing clinical research, the now adult's participation in the research is no longer regulated by the requirements of Subpart D regarding parental permission and participant assent.

Refer to *Office of Human Research Protections Frequently Asked Questions on Research with Children* and *Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements (nih.gov)*.

Protections for Wards

Subpart D mandates additional protections for minors who are wards of the State or any other agency, institution, or entity. Such minors can be enrolled in clinical research approved under sections 45 CFR part 46.406 and 21 CFR part 50.53, or 45 CFR part 46.407 and 21 CFR part 50.54 only if the research is either related to their status as wards or conducted at a location in which most of the minors enrolled as participants are not wards. To enroll children who are wards into clinical research that is approved under category 45 CFR parts 46.406 or 46.407 and 21 CFR parts 50.53 or 50.54, the DAIDS CRSs 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 as well as the DAIDS Protocol Team.

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

- 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 minor for the duration of the minor's participation in clinical research. (An individual may serve as advocate for more than one minor.)
- The advocate must not be associated in any way (except in the role as advocate or member of the IRB/EC) with the clinical research, the investigator(s), or the guardian organization.

Revision History

Revision	Summary of Changes
1.0	Original version; became effective on 1/19/2021
2.0	Removed requirement for CRS to submit SOP for Enrolling Minor for IRB/EC review.

References

1. U.S. Code of Federal Regulations, Title 21, Parts 11, 50, 54, 56, and 312
2. U.S. Code of Federal Regulations, Title 45, Part 46 and Subparts
3. International Council for Harmonisation Good Clinical Practice (ICH E6)
4. FDA Guidance: Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects [Oct 2009]
5. Office of Human Research Protections Frequently Asked Questions on Research with Children - Frequently Asked Questions | HHS.gov
6. Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements (nih.gov)