DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Allergy and Infectious Diseases
Division of Acquired Immunodeficiency Syndrome

Date: April 19, 2019

To: Clinical Trials Unit (CTU) Principal Investigators, Clinical Research Site (CRS) Leaders, CRS Coordinators, HIV/AIDS Network Leadership and Operations Centers

From: Office for Policy in Clinical Research Operations (OPCRO), Division of Acquired Immunodeficiency Syndrome (DAIDS)

Subject: Required Documentation for Pediatric Risk/Benefit Category 45 CFR 46.406 and 46.407

As you know, Institutional Review Boards (IRBs)/ Ethics Committees (ECs) have specific responsibilities to review all research supported by the U.S. Department of Health and Human Services (DHHS) involving children as participants and to approve those research studies satisfying conditions stated in the U.S. Code of Federal Regulations (CFR) Title 45 Part 46, Subpart D.

Per the DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements and DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements, for research studies including children or adolescents, DAIDS requires documentation of the IRB/EC designation of the pediatric risk/benefit category per 45 CFR 46, 404-407 and 21 CFR 50.51-54 and IRB/EC approval for involvement of children based on the determination specified by that pediatric risk/benefit category. This requirement applies to the initial and continuing/annual reviews of research protocols and to any subsequent reviews of full version protocol amendments and letters of amendments (LOAs) involving potential changes to study risks or benefits.

Effective May 1, 2019, when an IRB/EC determines the pediatric risk/benefit category is 45 CFR 46.407 or 45 CFR 46.406 for any research study, additional action and documentation will be required by DAIDS. Sites must provide the following, as appropriate:

For Pediatric Risk/Benefit Category 45 CFR 46.407:

If the risk/benefit category indicated on the IRB/EC approval letter for the research study is 45 CFR 46.407, sites will receive a notification from DAIDS Protocol Registration Office (PRO) to **CONFIRM the IRB's/EC's pediatric risk/benefit category designation. The DAIDS PRO review process will be stopped until the site confirms the IRB's/EC's pediatric risk/benefit category designation.**

Upon receipt of a notification from the DAIDS PRO, the CRS Principal Investigator (PI), Study Investigator of Record (IoR), or designee should contact the IRB/EC Chair/Director to either secure documentation of new pediatric risk/benefit category designation (first bullet below), or to confirm that the board/committee intended to select the risk/benefit category 45 CRF 46.407 and that the IRB/EC plans to move forward with the subsequent required steps (second bullet below):

- *If the risk/benefit category designation 46.407 was mistakenly selected, the site must request written documentation from IRB/EC with the corrected risk/benefit category designation. A copy of the relevant portion of the IRB/EC meeting minutes, signed and dated by the IRB/EC Chair or designee, documenting the IRB's/EC's risk/benefit category discussion and designation can be provided to the DAIDS PRO to meet the written documentation requirement. Sites must provide the documentation with the corrected risk/benefit category designation to DAIDS PRO in-order for the submission process to continue.*

- *If the IRB/EC confirms their decision of the 46.407 risk/benefit category selection, the CRS Principal Investigator (PI), Study Investigator of Record (IoR), or designee should refer to Appendix 1 of the DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements as this risk/benefit category requires a special level of DHHS review beyond that provided by the IRB/EC. Sites can also refer to the DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements and to the May 26, 2005 Guidance, "Children as Research Subjects and the HHS "407" Process." The DAIDS PRO review of a CRS's registration submission will be stopped pending a determination from the Secretary, HHS or his/her designee.*

For Pediatric Risk Category 45 CFR 46.406:

A site must have established written procedures that ensure adequate provisions are in place for:

- Soliciting parents' or guardians' permission, as required in 45 CFR 46.408 (i.e. permission is to be obtained from both parents unless: (1) One parent is deceased, unknown, incompetent, or not reasonably available; or (2) One parent has legal responsibility for the care and custody of the child).
- Soliciting documenting assent, when the IRB/EC requires that assent be obtained.
- Enrolling wards (e.g., orphans) with the appropriate documentation that: (1) recognizes the status of the individual child as a ward; (2) ensures communication of that status to the responsible IRB/EC; and (3) confirms the IRB/EC appointment of an advocate for the child/ward, in addition to any other individual acting as guardian or in loco parentis.

Refer to the DAIDS Policy DWD-POL-CL-007.02 DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements.

A site's written procedures to address the requirements of 45 CFR 46.406 should be kept in the site's regulatory files for verification by monitors.