Enrolling Children (including Adolescents) in Clinical Research Policy Tool: Recommended Language

This Tool provides recommended language for inclusion in DAIDS-supported, including DAIDS-Sponsored protocols that plan to enroll children (including adolescents who have not reached locally defined age of majority). This language may be included under an appropriate protocol section, such as "*Human Subjects Protections: 'Vulnerable Participants'* or *'Special Populations'*" header used below.

Recommended Language for Inclusion in Protocols Enrolling Children

HUMAN SUBJECTS PROTECTIONS

'Vulnerable Participants' or 'Special Populations':

It is the policy of NIH that children must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. As defined by HHS, children are "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." Per ICH E6(R2), children who take part in clinical research are considered vulnerable participants; therefore, special measures are needed to protect their rights and to protect them from undue risk. Interventions or procedures that present greater than minimal risk to participants must offer a sufficient prospect of clinical benefit to justify or outweigh exposure of children involved in research to such risk. Ethical principles are defined in the current legal and regulatory framework of regulatory authorities worldwide responsible for ensuring safeguards for the protection of children participating in research. HHS regulations in 45 CFR part 46 Subpart D, and for studies under FDA oversight, 21 CFR part 50 Subpart D, require additional safeguards and protections for children involved in research. Children may participate in research if all of the applicable requirements of 45 CFR part 46 Subpart D (and 21 CFR part 50 Subpart D for FDA-regulated research) and any applicable in-country laws and regulations are satisfied.

The IRB/EC of record must consider the potential risks and benefits to participants as described in 45 CFR 46 Subpart D. With respect to 45 CFR 46 Subpart D, the IRB/EC of record must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process, and the risk category assigned by the IRB/EC of record further determines the parental informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC of record may find that the consent of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC of record finds that the research is covered by 46.406 or 46.407, both parents must give their consent, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined locally). Per 45 CFR 46.409, children who are wards of the state or any other agency, institution, or entity can be included in research approved under 46.406 or 46.407. Additional special protections are required for children who are wards of the state or any other agency, institution, or entity. The IRB/EC of record must document their risk determination, and study sites should adapt the signature pages of their site-specific ICFs as needed to accommodate the parental consent requirements associated with the

IRB/EC determination.

Study sites must comply with the requirements of the DAIDS Policies available at: https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures. In addition to the US regulations cited above, sites must also comply with all applicable local and national and international guidelines and regulations. In cases where multiple different sets of requirements apply, the most stringent requirements must be followed.

Informed Consent (and Assent if applicable) Process

In obtaining and documenting informed consent, the site investigator must comply with the applicable regulatory requirements, ICH GCP guidelines, and ethical principles. The written informed consent form must be approved by the IRB prior to its use. Parental or legal guardian consenting requirements will depend on the IRB/EC risk determination and all IRB/IBC requirements will be followed.

Written informed consent will be obtained from emancipated minors who are legally able to provide informed consent. An emancipated minor is a person under the locally defined age of majority, who because of their unique circumstances (is married, pregnant or a parent, is self-sufficient, head of a child-headed family) has the legal rights of adults, including the right to consent to treatments or procedures involved in research. For adolescents who are not emancipated, permission from a parent or legal guardian will be required before an adolescent may provide her assent and undergo any procedures.

Where applicable, assent will be obtained with the amount of information and level of detail provided tailored to the age of the potential participant and guided by IRB/EC policies and procedures. Assent requirements for pediatric participants may vary across regions and countries; local regulations should be followed as appropriate. Each potential child participant who is not of legal age to provide independent informed consent is generally expected to take part in the informed consent process with their parent or legal guardian and both the assent of the participant and the permission of the parent or legal guardian will be required. If the participant does not provide assent, or the parent or legal guardian does not provide permission, the participant will not be enrolled in the study. Minor participants who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parent or legal guardian still wants them to participate.

Participants and their parent or legal guardian must be consented and assented to the most current version of the ICF(s) during their participation in the study. Minor participants must be consented again if they reach the locally defined age of majority during the course of the study, in order to continue participating. A copy of the informed consent, parental permission, and/or assent forms, as appropriate, must be provided to the participant and the participant's parent or legal guardian.