INFORMED CONSENT FORM AND PROCESS: GUIDANCE DOCUMENT

DIVISION OF AIDS (DAIDS)

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SEPTEMBER 2018
1. INTRODUCTION

The Division of AIDS (DAIDS) has established an informed consent (IC) manual to provide guidance to relevant stakeholders regarding the requirements for the development and implementation of informed consent forms (ICFs), Informed Consent (IC) documentation, and the informed consent process to ensure that all clinical research supported and/or sponsored by National Institute of Allergy and Infectious Diseases (NIAID) (DAIDS) is in compliance with the U.S. Department of Health and Human Services (HHS) regulations; the International Conference on Harmonisation (ICH), Guidance for Industry, E6 R2 Good Clinical Practice; DAIDS Clinical Research Policies; and when applicable, the U.S. Food and Drug Administration (FDA) regulations. The manual identifies required content areas for ICFs and provides guidance as to the level of detail required. It references regulations, guidance documents, NIH, NIAID, and DAIDS policies and standard procedures, and current best practices that should be consulted during the development of ICF(s) and related documents, and during the implementation of these documents. All DAIDS policies, standard procedures, guidance documents, and manuals referenced in this guidance document/manual can be accessed at the NIAID website: DAIDS Clinical Research Policies and Standard Procedures Documents.

Along with the Informed Consent Process Policy and the Informed Consent Process Guidance, there are tools such as the DAIDS Informed Consent Templates and Informed Consent SOP Examples to assist protocol teams, protocol chairs/co-chairs, DAIDS networks, staff, and other relevant stakeholders with the development of protocol sample ICFs and site-specific ICFs. There are also informed consent companion documents such as the Protocol Documents Policy and Manual, the Essential Documents Policy and Guidance Document, and the Protocol Registration Policy and Manual.
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2. DEFINITIONS

**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. [45 CFR §46.402(a) and 21 CFR §50.3(o)]

**Clinical Research:** Research conducted on participants, material, or data of human origin with an identifiable person as the source. Clinical research includes exploratory, behavioral, and observational studies. All clinical trials are a subset of clinical research. (DAIDS)

**Clinical Research Site (CRS):** Distinct locations (e.g., hospitals, outpatient clinics, health maintenance organizations, community health centers, private practices, clinics) supported and/or sponsored by NIAID (DAIDS) where qualified professionals conduct clinical research in accordance with good clinical practice (GCP) and applicable regulations. (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 research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. (NIH)

**Clinical Trial Insurance (CTI):** Clinical trial liability insurance is a form of professional liability insurance that protects clinical trial sponsors, investigators, institutions and administrators from risks they assume when conducting clinical trials. The coverages of a policy are tailored to the policyholder’s specific needs (i.e. trial protocol, informed consent, site locations, in country regulatory requirements, local ethics committee requirements, etc.) and will vary in each instance. The policy may include coverage against any bodily injury or property damage that a drug, device, or treatment may causes, as well as liability coverage for any professional duties that an organization or its employees may have in the conduct of performing the clinical trials. (DAIDS)

**DAIDS Protocol Registration Office (PRO):** An office within the DAIDS Regulatory Support Contract (RSC) that receives and processes all protocol registration materials for DAIDS. (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)

**DAIDS supported:** Clinical research activities would be considered to be supported by NIAID (DAIDS) under one or more of the following circumstances:

- NIAID (DAIDS) provides direct funding to an institution via a grant, contract or cooperative agreement for the clinical research activities; or (b) indirect funding via a subcontract executed under a NIAID (DAIDS)-supported award to another institution; and/or
- NIAID (DAIDS) provides other tangible support for the clinical research activities which includes, but is not limited to, regulatory support, site monitoring services, study product supply, management and distribution services; and/or
• 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)

Fetus: The product of conception from implantation until delivery [45 CFR part 46.202(c)].

Informed Consent Form (ICF): A document that provides the elements of informed consent as found in 21 CFR 50.25 and 45 CFR 46.116 (DAIDS)

Informed Consent (IC) Process: A process by which a participant voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the trial that are relevant to the participant’s decision to participate. (ICH E6)

Incidental finding (IF): A finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study. (DAIDS)

Institutional Review Board/Ethics Committee (IRB/EC): The board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of participants in research. IRB/EC reviewing DHHS sponsored research must be registered with OHRP and identified on the institute FWA. (DAIDS)

Interventions: Physical procedures by which data are gathered and manipulations of the participant or the participant's environment that are performed for research purposes. (DAIDS, modified from 45 CFR 46.102)

Investigational device exemption (IDE): An approved investigational device exemption permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device. (FDA)

Investigator of Record (IoR): The individual at the CRS responsible for ensuring that a clinical trial is conducted in accordance with the protocol, applicable U.S. federal regulations, in-country regulations and any provisions imposed by the reviewing IRB/EC/other regulatory entity. This person is the signatory for the Form FDA 1572 for studies conducted under an IND or the DAIDS Investigator of Record Agreement for non-IND studies. (DAIDS)

Letter of Amendment (LoA): A revision to a protocol made by the Protocol Team/Chair/Awardee through a letter that requires DAIDS final approval/sign-off before implementation. Changes described in a LoA are listed in a document that is separate from the protocol document itself and will NOT result in the change to the DAIDS protocol version number. (DAIDS)

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. [45 CFR §46.102(i) and 21 CFR §50.3(k)]

Neonate: A newborn [45 CFR part 46.202(d)]

Nonviable neonate: A neonate after delivery that, although living, is not viable [45 CFR part 46.202(e)]
Pregnancy: The period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery [45 CFR part 46.202(f)].

Protection of Participants, Evaluation, and Policy Branch (ProPEP): A branch of DAIDS within the Office of Clinical Research Policy and Resources (OPCRO). ProPEP provides consultation and expertise to address complex human subjects protection regulatory issues. (DAIDS)

Protocol Chair/Co-Chair: Individual(s) who is/are responsible for developing and conducting the study. (DAIDS)

Protocol Informed Consent Form (ICF): An informed consent form developed by the protocol team for a specific protocol. See also Sample Informed Consent Form. (DAIDS)

Protocol Registration: The process established by DAIDS to ensure that all sites participating in NIAID (DAIDS) supported and/or sponsored clinical research that is reviewed by a DAIDS Scientific Review Committee conduct the research in accordance with requirements for human subjects protection and the use of investigational new drugs (where applicable). The process includes initial protocol registration, amendment registration, continuing review documentation, deregistration and submission of other required documents. (DAIDS)

Protocol Registration Team (PRT): A Team within OPCRO responsible for managing the Protocol Registration (PR) System, which includes oversight of the DAIDS PRO. (DAIDS)

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 may be involved as members of this team. (DAIDS)

Regulatory Entity (RE)/Approving Entity: Any group other than the reviewing IRB/EC responsible, for reviewing and/or approving a clinical research protocol and site-specific ICFs prior to implementation at a site. For example, in some states within the U.S., institutional approvals are required since these states have research regulations in addition to the federal human subjects protection regulations detailed in U.S. federal regulations (45 CFR §46). In addition, at many non-U.S. sites, other approvals may be required in addition to the reviewing IRB/EC approval, which include but are not limited to approvals from ministry of health, national regulatory agency, in-country drug control council, national IRB/EC, or other government agency. (DAIDS)

Sample Informed Consent Form (ICF): An informed consent form developed by the protocol team for a specific protocol that will help guide participating sites in the development of their site-specific informed consent. This term is mainly used for multi-site studies. See also Protocol Informed Consent Form. (DAIDS)

Scientific Review Committee (SRC): A reviewing body within DAIDS to review the concepts and protocols developed by various programs within DAIDS (e.g., CSRC and PSRC). (DAIDS)

Site-Specific Informed Consent Form (ICF): An informed consent form developed by a participating site based upon the sample informed consent form which is reviewed and approved by the site’s designated IRB/IEC and is used to consent subjects at the site for a specific clinical trial. (DAIDS)
Study products: Any drug, biologic, vaccine, radiopharmaceutical, item or device that are either provided for the study or identified in the protocol as being a study product. (DAIDS)

Vulnerable participants: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. (ICH E6).

For additional definitions, SEE the DAIDS Glossary.
## 3. LIST OF ABBREVIATION

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
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<tr>
<td>CDRH</td>
<td>Center for Devices and Radiological Health</td>
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<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
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<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
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<tr>
<td>CoC</td>
<td>Certificates of Confidentiality</td>
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<tr>
<td>CQMP</td>
<td>Clinical Quality Management Plan</td>
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<tr>
<td>CRS</td>
<td>Clinical Research Site</td>
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<tr>
<td>CTA</td>
<td>Clinical Trials Agreement</td>
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<tr>
<td>CTI</td>
<td>Clinical Trials Insurance</td>
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<tr>
<td>DAIDS</td>
<td>Division of AIDS</td>
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<tr>
<td>dbGaP</td>
<td>Database of Genotypes and Phenotypes</td>
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<tr>
<td>DoD</td>
<td>Delegation of Duties</td>
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<tr>
<td>EC</td>
<td>Ethics Committee</td>
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<tr>
<td>eIC</td>
<td>Electronic Informed Consent</td>
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<tr>
<td>FDA</td>
<td>(U.S.) Food and Drug Administration</td>
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<tr>
<td>FDAAA</td>
<td>(U.S.) Food and Drug Administration Amendments Act</td>
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<tr>
<td>FWA</td>
<td>(U.S.) Federalwide Assurance</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GDPR</td>
<td>(European) General Data Protection Regulation</td>
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<td>GDS</td>
<td>Genomic Data Sharing</td>
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<tr>
<td>GINA</td>
<td>Genetic Information Nondiscrimination Act</td>
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<tr>
<td>GWAS</td>
<td>Genome-Wide Association Studies</td>
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<tr>
<td>HHS</td>
<td>(U.S.) Department of Health and Human Services</td>
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<tr>
<td>HIPAA</td>
<td>(U.S.) Health Insurance Portability and Accountability Act</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HSP</td>
<td>Human Subjects Protections</td>
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<td>IB</td>
<td>Investigator's Brochure</td>
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<td>IC</td>
<td>Informed Consent</td>
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<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
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<tr>
<td>IDE</td>
<td>Investigational Device Exemption</td>
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<tr>
<td>IF</td>
<td>Incidental Finding</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug Application</td>
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<tr>
<td>IoR</td>
<td>Investigator of Record</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>IRR</td>
<td>Individual Research Result</td>
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<tr>
<td>LAR</td>
<td>Legally Authorized Representative</td>
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<tr>
<td>LoA</td>
<td>Letter of Amendment</td>
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<tr>
<td>MO</td>
<td>Medical Officer</td>
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<tr>
<td>NIAID</td>
<td>(U.S.) National Institute of Allergy and Infectious Diseases</td>
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<tr>
<td>NIH</td>
<td>(U.S.) National Institutes of Health</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>NLM</td>
<td>(U.S.) National Library of Medicine</td>
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<td>OHRP</td>
<td>(U.S.) Office for Human Research Protections</td>
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<tr>
<td>PI</td>
<td>Package Insert</td>
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<tr>
<td>PRO</td>
<td>Protocol Registration Office</td>
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<tr>
<td>QA/QC</td>
<td>Quality Assurance/Quality Control</td>
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<tr>
<td>RE/AE</td>
<td>Regulatory Entity/Approving Entity</td>
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<tr>
<td>RSC</td>
<td>Regulatory Support Center</td>
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<tr>
<td>SACHRP</td>
<td>(U.S.) Secretary’s Advisory Committee on Human Research Protections</td>
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<tr>
<td>SAHPRA</td>
<td>South African Health Products Regulatory Authority</td>
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<tr>
<td>SIC</td>
<td>Sample Informed Consent</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SRC</td>
<td>Scientific Review Committee</td>
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<tr>
<td>STI</td>
<td>Sexually Transmitted Infection</td>
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<td>WHO</td>
<td>World Health Organization</td>
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4. GUIDANCE FOR DEVELOPING PROTOCOL INFORMED CONSENT FORMS

Informed consent is a process that includes ongoing communication and information exchange between the participant and an investigator/research team. This process often includes a written informed consent form (ICF), Institutional Review Board (IRB)/Ethics Committee (EC) -approved participant recruitment materials, verbal instructions, question/answer sessions and tools to measure participant understanding. Often, an informed consent form (ICF) is used to inform participants about the study and to document the informed consent process. The informed consent form must provide sufficient information for a potential participant to make an informed decision about participating in a study.

4.1. Ethical Foundation – The Belmont Report

The Belmont Report describes three fundamental ethical principles for involving individuals in clinical research: respect for persons, beneficence, and justice. These three principles are the basis for the United States Department of Health and Human Services (HHS) human subjects protection regulations.

- "Respect for Persons" is centered on the participant’s right to autonomy and the ability to make a choice, and the requirement to protect those participants with diminished autonomy. This principle underlies the requirement to obtain legally effective informed consent.

- "Beneficence" is related to protecting research participants from harm and making efforts to safeguard their well-being. This principle is centered on the perspective of “do no harm” by minimizing risks to participants and maximizing benefits to society.

- "Justice" is focused on the distribution of the burdens and benefits of research. This principle is related to the equitable selection of research participants and the prevention of exploitation of vulnerable populations.

Three fundamental elements of informed consent—The Belmont Report

- "Information" needed to make an informed decision about study participation;
- "Comprehension" or participant’s understanding of the information; and
- "Voluntariness" or the participant’s capacity to decide whether or not to participate in the research, free of coercion and/or undue influence.

4.2. HHS, FDA, and ICH E6 (R2) Informed Consent Regulatory Requirements

All research involving human participants that is conducted or supported by the Department of Health and Human Services (HHS) is subject to the U.S. Code of Federal Regulations at 45 CFR 46, including NIAID (DAIDS) supported and/or sponsored non-exempt clinical research. Therefore, NIAID (DAIDS) protocol ICF(s) must be written in compliance with the 45 CFR 46.116., which clearly discusses the requirement to minimize the possibility of coercion or undue influence. In other words, the importance of focusing the ICF(s) on true voluntariness. The Belmont Report states that “An agreement to participate in research constitutes a valid consent only if voluntarily given.” Thus, all ICFs must be free of coercion and undue influence, as defined by the report: “Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance; Undue influence, by contrast, occurs through an offer of an
excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that
would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.” Thus, all ICF(s) offered by investigators should give each participant the opportunity to consider if he/she wants to participate in the study and should be a process and a form that minimize the possibility of coercion or undue influence.

Another important aspect of this voluntariness is that the consent process should not include any exculpatory language. Language used to ask the study participant to “waive or appear to waive any of his or her legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agents from liability for negligence.” The regulations consider exculpatory language to be “language that has the general effect of freeing or appearing to free an individual or an entity from malpractice, negligence, blame, fault, or guilt.” (21 cfr section 50.20 and 45 cfr 46.116)

ICFs must also be in compliance with the International Conference on Harmonisation (ICH), Guidance for Industry, and E6 (R2) Good Clinical Practice, section 4.8. This section entitled Informed Consent of Trial Subjects, contains similar required informed consent form elements as required by HHS and FDA (basic and additional elements) (E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry).

Furthermore, those protocols that are subject to FDA regulations must also adhere to 21 CFR 50.25 (CFR - Code of Federal Regulations Title 21).

Reviewing IRBs/ECs have the final authority for ensuring the adequacy of the information in the IC documents.

4.3. Basic Elements of Informed Consent

45 CFR 46.116(a), 21 CFR 50.25(a), and ICH E6 (R2), section 4.8.10. In seeking informed consent, information related to the eight required basic elements as per §46.116(a) and §50.25(a) must be provided to each participant:

4.3.1. Purpose and Procedures

“A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.”

Potential participants need to be clearly informed that the study involves research, and that study participation is primarily to contribute to science rather than to receive personal medical treatment. Also, participants must be informed about the study’s purpose. For instance, IC documents should include information related to the primary objective(s) of the study, should include “safety” even if it is a secondary objective (if applicable), and should indicate if a study intervention is experimental (if applicable).

Additional information to be incorporated into IC documents includes but is not limited to:

- Reasons for a potential participant’s selection (e.g., HIV-infected, CD4 count ≥500)
4.3.2. Risks and Discomforts

“A description of any reasonably foreseeable risks or discomforts to the subject.”

Research-related risks have been categorized as physical, psychological, social, legal, or economic, occurring as a result of participation in a research study, and ranging from minimal to significant. As per U.S. regulations, IC documents should describe any reasonably foreseeable risks corresponding with the risks communicated in the protocol, especially risks that are more likely to occur, those that are serious, and those that may carry significant risk of morbidity or mortality. IC documents can include a description of the methods that will be used to mitigate risks.

4.3.2.1. Risk information associated with the study product(s)/intervention(s)/strategy(ies) to be incorporated into IC documents includes:

- Risk information described in the protocol, package insert (PI), Investigator’s Brochure (IB), and/or relevant publications, as well as risks associated with the study procedures (e.g., phlebotomy, pelvic exams, DEXA scans). If long-term safety studies are ongoing at the time the study is implemented, participants should be informed that studies that may identify potential risks have not yet been completed.
  
  o Use the DAIDS-approved core risk information lists, if available, for study product(s) risk information that should be included in IC documents. Risk information language used in the related DAIDS-approved core risk list(s) may be modified by the protocol team. However, all key concepts listed in the DAIDS core risk list(s) should remain in the informed consent form documents.
  
  o Consult all relevant up-to-date sources of risk information, including the most recent package insert (PI) for FDA approved products, Investigator’s Brochure (IB) for investigational products, etc. to obtain the most current information on study product risks, interactions, contraindications, and precautions. Address the updated information in the protocol as well as in the IC documents.
  
  o Revise risk information in the protocol and IC documents as appropriate during the course of the study, based on interim safety information and other relevant
NOTE: Additional risks for a particular study product can be added to the IC documents, if this information is described in the body of the protocol.

- Consider describing the probability, frequency, and severity of potential risks as follows:
  - "Common, some may be Serious" - Occurring in greater than 20% of participants receiving the study agent(s).
  - "Occasional, some may be Serious" - Occurring in 4% to 20% of participants receiving the study agent(s).
  - "Rare, and Serious" - Occurring in 3% or fewer participants and that are not considered reasonably foreseeable but are serious.
  - "Possible, some may be Serious" - Relating to IND agents for which the frequency of individual risks has not yet been determined.

SEE: NCI INFORMED CONSENT TEMPLATE FOR ADULT CANCER TRIALS PAGE 33: NCI Informed Consent Template for Adult Cancer Trials

NOTE: Descriptions of risks of individual drugs or agents not specified in the protocol (e.g., drugs/agents not provided through the study) do not need to be included in consent documents; however, general statements regarding common risks for relevant drug classes or referral to package inserts could be included.

4.3.2.2. Additional risk information considerations to be addressed:
- Risks related to study participation (e.g., due to changes to a participant’s regular/stable medication regimen; developing drug resistance due to sub-optimal treatment and consequential limitation of future treatment options; development of vaccine-induced seropositive test result after receiving an experimental preventative HIV vaccine; risks related to randomization; risks of long-term effects). Consider including potential risks related to participating in more than one study (e.g., study product interactions, etc.).
- Risks related to differences in efficacy of the study products, based on the data available at the study’s commencement (e.g., difference in efficacy may impact a participant’s risk of HIV acquisition).
- Risks such as social impact events (e.g., inadvertent disclosure of study participation resulting in stigmatization or discrimination), as well as legal and economic risks (e.g., unintentional disclosure of drug or alcohol use or illegal activities; loss of employment; procedures or treatment billed to a participant’s insurance company).
- Risks related to the future research use of samples and associated health information (e.g., secondary use) as well as risks associated with general and genomic data-sharing. Oftentimes, such studies do not involve interaction with research participants. However,
there are potential risks, many of which are informational, that may increase as technology evolves. These risks include but are not limited to:

- Inappropriate disclosure of information leading to privacy and confidentiality risks (e.g., unauthorized exposure of personal identifiers, breach of confidentiality, etc.)
- Participant re-identification, including the combined use of publicly available data and genomic data
- Emotional, social, or financial consequences related to privacy and confidentiality breaches
- Discrimination related to privacy and confidentiality breaches
- Psychological risks such as stress, anxiety, invasion of privacy, etc.
- Potential risks to others who are not study participants (e.g., live-attenuated vaccine where close proximity to a participant may present a risk to an immunocompromised household member).

- Risks unknown at the study’s commencement.
- Risks particular to vulnerable populations who may be susceptible to coercion or undue influence, etc.

4.3.3. Benefits

“A description of any benefits to the subject or to others which may reasonably be expected from the research.”

IC documents should describe any reasonably foreseeable, potential direct benefits related to the study product(s), intervention(s), and/or strategy(ies), if any. Additionally, IC documents should explain any potential ancillary benefits to the study participant (e.g., additional monitoring, increased health awareness, access to early treatment for any secondary diagnosis) and to society (e.g., future knowledge about the condition), if any.

If there is no prospect of direct benefit from study product(s)/intervention(s)/strategy(ies), such as in Phase I studies, IC documents should state this information clearly. Furthermore, the benefits statement in IC documents must correspond with the benefits described in the protocol, must be clear and balanced, and must not be overstated.

**NOTE:** Participant compensation is not considered a “benefit”; compensation is usually provided to offset the time, inconvenience, and expenses related to study participation, not as “payment” for participation.

4.3.4. Alternative Treatment and Procedures

“A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.”

IC documents should discuss the various alternatives to participation in the study and should contain sufficient information for a potential participant to make an informed decision. These alternatives may include any treatment or procedures available outside of the research study...
under consideration, including the established standard treatment, especially if the study involves the administration of investigational drugs or the use of new therapeutic procedures. For example, in HIV treatment studies, antiretroviral medication(s) may be available through a participant’s family doctor or clinic without the need to participate in a study. The alternatives section should clearly state the possible choices, including the important potential benefits and risks of these alternative(s). Alternatives to study participation can include: no treatment, standard of care therapy, other experimental treatments, or some or all of the study treatment, but without participating in the study. Additional information may include notifying participants:

- That standard treatment will be withheld as a result of study participation
- That there are no alternative treatments
- That one alternative is not to participate in the study (for both participants who have the underlying condition under study as well as normal, healthy volunteers)
- That participation in a particular study may preclude participation in other studies now and/or in the future (e.g., receiving a preventative HIV vaccine may make a volunteer ineligible for other HIV vaccine studies)
- That participation may make the participant ineligible for specific standard of care options (e.g., a particular class of antiretroviral agents)

4.3.5. Confidentiality

“A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.”

IC documents should identify all entities that may have access to study records, including the possibility that the FDA and other regulatory entities (RE) may inspect the records for FDA-regulated studies. Entities may include the study sponsor such as the NIH, pharmaceutical company(ies) providing study medications and/or supporting the study, the IRB/EC/RE, OHRP, the network supporting the study, study staff, and study monitors and their designees. Specifically, participants must be informed that “U.S., local and international regulatory authorities/entities” may also review study records. Additional confidentiality issues may include informing participants:

- If any data will be made available to others (e.g., associated health information that may be provided to investigators when conducting future research with leftover samples)
- If a Certificate of Confidentiality has been obtained which protects the investigators from involuntary release of participant information (e.g., subpoena) (SEE: Section 4.6.1)
- If audio or videotape recording, photographs, and/or movies will be taken as part of the study, the duration of time they will be kept, how confidentiality will be maintained, and whether they will eventually be erased or destroyed (timing dependent on the Storage and Retention of Clinical Research Records Policy)
- About any steps that will be taken to maintain confidentiality and privacy (e.g., keeping paper study records in a secure and locked place; not using identified information in publications,
meetings, or stored samples; using a code to identify participants and samples; securely
storing the participant identification code (PID) list, maintaining it separately from the
research records, and limiting access to the PID list)

In addition, DAIDS requires clinical research sites (CRSs) to verify the ages and identities of
potential participants before enrollment and throughout the duration of their study
participation. Verification includes data sharing among DAIDS and non-DAIDS sponsored clinical
research sites. Data sharing procedures must be done in such a way that maintains participants’
confidentiality. Participants should be informed about any data-sharing procedures pertaining
to co-enrollment procedures, and any related risks.

**SEE: The Age and Identity Verification and Co-Enrollment Prevention Policy**

4.3.6. Compensation, Treatment of injury

“For research involving more than minimal risk, an explanation as to whether any compensation
and an explanation as to whether any medical treatments are available if injury occurs and, if so,
what they consist of, or where further information may be obtained.”

OHRP recommends the use of the “healthy person” standard when determining what is
considered minimal risk--§46.102(i): “Minimal risk means that 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.”

IC documents must include a statement about research-related injury, even if there is no
mechanism for compensation. These documents should describe any compensation and medical
treatment available through the study and at the local level, as compensation and treatment may
vary depending on the protocol’s Clinical Trials Agreement (CTA), individual participant, policies
of the institution and/or sponsor, CRS capabilities, geographic area, and/or local IRB/EC and in-
country requirements (e.g., laws, regulations, etc.). IC documents should also clarify for which
type(s) of research-related injury (e.g., physical such as liver damage, psychological such as
emotional distress, social such as family discrimination, financial such as lost wages, etc.)
participants may receive compensation. IC documents, when applicable, should include relevant
information about what research-related treatment is available at the site as well as any referrals
for care.

However, if the institution and/or site will not be providing compensation for research-related
injury, the IC document needs to specifically state this. In this instance, the ICF must also state
that the NIH does not have a mechanism to provide direct compensation for research related
injury.

If Clinical Trials Insurance (CTI) is an in-country requirement, the ICF must include related
information. CTI is a policy that may include coverage against any bodily injury or property
damage that a drug, device, or treatment may cause to a participant (SEE: Definition of CTI).
Similarly, ICH E6 (R2) section 5.8.1 requires sponsors to provide compensation for participants(s)
for research-related injury for studies conducted in countries where this is a requirement by
regulation. Participants should be informed about the availability of CTI, and the types of “injury” that is covered (e.g., physical, psychological, social, financial, etc.). (SEE: Section 5.2)

When applicable, a site can adopt and revise the following language for its site-specific ICF:

“Consistent with in-country guidelines (add as appropriate: regulations, laws, institutional policies, etc.), our clinic has purchased insurance to cover your medical treatment for study-related physical injuries that you are experiencing from participating in this study. We can also provide compensation for (add/clarify as appropriate: type of non-physical research-related injury compensation coverage provided by the site’s policy, e.g., psychological such as emotional distress, social such as family discrimination, financial such as lost wages, etc.).”

**NOTE:** The regulations do not limit research-related injury to "physical injury"

### 4.3.7. Problems and Questions

“An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject.”

Each IC document is expected to have at least two names with local telephone numbers for contacts to answer questions in these specified areas.

The contact for questions related to the research needs to be someone who would be knowledgeable about the research, such as the investigator or his/her designee.

The contact for questions related to participant’s rights should not be a member of the research team because of potential conflicts of interest and because participants may be uncomfortable identifying possible problems to someone who is a member of the research team.

The contact for questions related to the rights of participants or research-related injuries could be the IRB/EC, an ombudsman, an ethics committee, or other informed administrative body.

Contact information should include the contact names or offices as well as their telephone numbers, including any 24-hour contact information (if applicable).

### 4.3.8. Voluntary Participation Statement

“A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.”

Participants must be informed that they may decline to take part in a study and/or may decide to withdraw from the study at any time. In either case, the participant will not incur any penalty or loss of benefits in which they are already eligible at the CRS outside the research.

Participants must be informed about any foreseeable issues should they decide to withdraw from the study. Include any special withdrawal procedures that are recommended in order to ensure the participant’s safety and/or any health consequences if the participant should stop the study product or study intervention early. Participants should be informed that any data that were
collected about them prior to their withdrawal from the study will still be part of the study since their deletion would impact the integrity of the research (for those studies subject to FDA regulations).

4.4. Additional Elements of Informed Consent as per §46.116(b) and §50.25(b)

The HHS and FDA regulations identify additional elements of informed consent. It is up to each reviewing IRB/EC/RE to determine whether some or all of the additional elements listed below need to be included in the IC documents for a study, based on the nature of the research and the local context.

**NOTE:** many of the HHS and FDA additional elements are included in ICH E6 (R2) section 4.8.10 and, therefore, should be included in IC documents.

Additionally, an IRB/EC/RE may require information to be included in IC documents beyond the basic and additional elements described in §46.116 and §50.25.

When appropriate, provide one or more of the following additional elements and their related information to each participant.

4.4.1. Risks to Participant/Risks to Fetus during Pregnancy

“A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.”

- Participants should be informed that a study product/intervention/strategy may involve risks to the participant/embryo/fetus that are not known at the time at the study’s start.

- Participants should be informed, if applicable, if long-term bench and animal testing and any related “first in human” studies have not yet been completed by the study’s start since these studies may identify additional potential risks to the participant/embryo/fetus.

- Participants should be informed about any pregnancy, lactation, and/or reproductive-related risks (e.g., birth defects; risks related to ongoing fetal or infant exposure to the study drug), based on the study product(s) (including package inserts and IBs), intervention(s), and/or strategy(ies). IC documents need to clearly describe any known risks as well as any risks that are currently unforeseeable to the participant or to the embryo or fetus should pregnancy occur. Additionally, IC documents should include methods to mitigate potential risks, which may include informing:

  o Women of childbearing potential to avoid pregnancy or nursing during or after participating in a study to protect the health and safety of the mother and/or embryo/fetus/infant

  o Males to avoid impregnating a woman if there is a risk of transferring a study product via semen

  o Participants not to partake in a conception process for a specified time before, during and/or after study participation
o Participants about the number, type(s), and length of time contraception may be required (e.g., 2 forms of contraception, including one that is a barrier method, 21 days prior to entering the study until the last study visit)
o Participants about pregnancy testing, including the timing and frequency of these testing; testing may occur before, during, and/or after the study
o Participants about the need to monitor for pregnancy outcomes, as applicable (e.g., Antiretroviral Pregnancy Registry; follow-up visits/phone calls for pregnancy outcome information)

**SEE:** The Therapeutics Research Program Guidance for the Development of Protocol Procedures to Address Reproductive Risk document for additional information ([DAIDS Therapeutics Research Program Guidance for the Development of Protocol Procedures to Address Reproductive Risk](#)).

### 4.4.2. Involuntary Termination of Study Participation

“Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject's consent.”

Participants should be informed about any circumstances that may result in their involuntary termination from study participation. If study participation is discontinued, the participant should be told about the reason(s), any other available treatment or research options, and any plans to follow the participant for safety reasons, if applicable. Describe any anticipated conditions which can lead to involuntary termination, including but not limited to:

- The participant is unable to follow the study’s requirements (e.g., repeatedly misses study visits)
- The participant no longer meets the study’s eligibility criteria (e.g., subsequently becomes HIV-infected in a preventative vaccine study; needs a medication that is prohibited while on study)
- The CRS withdraws from the study and there is no CRS in the vicinity to accept the participant as a transfer
- The investigator believes it is in the participant’s best interest not to continue study participation (e.g., the participant is having severe side effects from the study product)
- The study is stopped or canceled by the study sponsor (e.g., U.S. NIAID, U.S. FDA, U.S. OHRP, EMA, the reviewing IRB/EC/RE)
- The participant’s parent/legal guardian withdraws his/her permission for the child’s study participation

### 4.4.3. Additional Costs

“Any additional costs to the subject that may result from participation in the research.”

IC documents need to describe any study-related costs, which may include:

- Costs such as loss of income related to time off from work needed to participate in the study, transportation costs, childcare costs, etc.
• Costs of study lab tests, procedures, exams, and/or products that may be charged to the participant, the participant’s insurance, or any other reimbursement mechanism

• If applicable at the local level, costs to participants related to insurance or other forms of reimbursement not paying for their medical care due to their study participation, even if this care is the standard of care they would have received outside of the study

• If applicable at the local level, costs to participants related to insurance or other forms of reimbursement not paying for any care due to research-related complications or injuries

• If applicable at the local level, costs to participants related to any deductibles or co-payments in the event their insurance is charged

4.4.4. Early Withdrawal from Study/ Orderly Termination

“The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject.”

Inform participants about the following issues, including but not limited to:

• Any potential anticipable/known adverse effects of stopping the study product(s) and/study intervention(s) early

• Any special withdrawal procedures that are recommended to ensure the participant’s safety and why these procedures are important (e.g., gradual withdrawal of the study product; follow-up safety visits even though the participant has stopped receiving study product)

• If applicable at the local level, any impact of premature discontinuation on study compensation/reimbursement

4.4.5. New Findings

“A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.”

Participants should be informed, in a timely manner, about any significant new findings during the course of an ongoing study that may impact a participant’s willingness to continue study participation. Related issues that should be considered include but are not limited to:

• Any unexpected adverse events or risks and/or adverse events that are occurring at a greater frequency or severity than what was previously stated in the IC document(s) resulting in a change to the risk/benefit profile of the study (e.g. an increase in the magnitude of known suspected risks, a decrease in the expected benefit)

• Any interim findings from the ongoing study or external studies that show statistically significant survival/efficacy/improvements from a particular study product/intervention/strategy

• Any changes in the level of discomfort or other inconvenience

• Any new regulatory approval (e.g., FDA, MCC/SAHPRA, EMA) of study products/intervention used in the study
• Any new alternative treatment options that become available
• Any major changes to the study based on these new findings such as revised/additional study procedures, changes in the dose or frequency of the study product, modifications to the study design including extended follow-up and/or additional study visits, changes to compensation/reimbursement or costs related to study participation, etc.
• Methods of communicating new findings to participants include but are not limited to: in person, documented phone contact, re-consent with a revised informed consent document, consent addendum, and “Dear Participant” letters (SEE section 6.6.3).

4.4.6. Number of Participants

“The approximate number of subjects involved in the study.”

Participants should be informed about the approximate number of participants involved in the specific research study, including why this number is important especially if this information may impact his/her decision to participate (e.g., the study is a first in human study or a Phase 1 study; a small number of participants may jeopardize confidentiality).

Participants could be informed about the countries, the number of sites, and the approximate number of participants at each site in multi-site, multi-national studies. Potential participants may want to know this information prior to deciding to join the study (e.g., to allay any potential concerns about exploitation if a riskier study is only being conducted in resource-limited settings).

SEE: Section 8.0 for information related to the new Informed Consent elements required by the Revised Common Rule (To be implemented January 2019).

4.5. Additional Pregnancy-Related Informed Consent Form Requirements and Considerations

4.5.1. Pregnancy Prevention Considerations

If applicable, advise participants of any pregnancy-prevention measures (e.g., use of contraception, avoidance of conception) to be taken while on the study. ICF(s) should include contraception and conception information based on the available reproduction toxicity data of the study intervention(s)/agent(s), the FDA-Use-in-Pregnancy drug categories (if applicable), and/or the revised FDA pregnancy, lactation, and reproductive potential labelling requirements (e.g., the number and type of required contraceptive methods and the length of time of their required use).

4.5.2. Subsequent Pregnancy Considerations

Despite instructions to avoid pregnancy for a time before, during or following study participation and the use of pregnancy prevention measures, pregnancy may occur. The protocol and ICF(s) need to describe any procedures to be followed in the event that a female participant subsequently suspects or becomes pregnant while on study. Considerations include:

• Premature study discontinuation procedures for participants who become pregnant after study enrollment (e.g., off study product(s), intervention(s), and/or strategy(ies) and off study participation)
• “Pregnancy visit” procedures, outlining appropriate modifications to study procedures and any additional safeguard procedures (e.g., discontinuation of study product(s)/intervention(s), conditions under which continuation of the intervention may occur, alterations in study evaluations such as limiting radiation exposure or blood volumes, ultrasounds and other procedures to monitor fetal growth). ICF(s) should indicate whether the participant will be allowed to continue to receive the study product(s)/intervention(s) and/or strategy(ies). Additionally, ICF(s) should provide any other guidance relevant to the study product/intervention and pregnancy and/or breastfeeding. (e.g., the participant may be allowed to continue to receive study product during pregnancy but will not be allowed to breastfeed)

• Study-specific pregnancy consent form and informed consent process that reflects any additional risk/benefit considerations, if applicable

**SEE:** FDA Draft Guidance 4/2018:
- Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry;
- Pregnancy and Lactation Labeling (Drugs) Final Rule;
- FDA Draft Guidance 12/2014:
- Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry

4.5.3. Pregnancy Outcome Monitoring Considerations

The IC documents need to include information regarding how pregnancy outcomes may be monitored, including:

• Phone and/or in person study clinic visit follow-up to ascertain the pregnancy outcome

• Rollover study or pregnancy registry/follow-up study (e.g., MTN 016) for the female and/or the infant/child

• Voluntary or required pregnancy registries for participant’s receiving antiretrovirals or other products for which such registries exist (e.g., pregnancy exposure registries such as the Antiretroviral Pregnancy Registry, The Antiretroviral Pregnancy Registry)

**SEE:** DAIDS Clinical Trial Protocol Documents Manual section 14.3

4.5.4. Replacement Feeding/Breastfeeding ICF Considerations

As determined by the study product(s), intervention(s), and/or strategy(ies), participants able to become pregnant are sometimes instructed to avoid breastfeeding during or after participating in a study to protect the health and safety of the infant. Permitting breastfeeding may be based on current WHO or applicable in-country infant feeding guidelines. If relevant, ICF(s) need to address breastfeeding/replacement feeding issues as well as any related risks and/or benefits, based on the information included in the protocol. Some considerations include:
If breastfeeding is permitted during study participation, the ICF(s) need to include relevant information for participants who plan to breastfeed their infants while on study.

When replacement feeding is acceptable, feasible, affordable, sustainable, and safe, avoidance of all breastfeeding by HIV-infected mothers is currently recommended; however, if formula feeding is permissible, include pertinent information in the ICF(s) (e.g., whether safe water to reconstitute formula needs to be readily available).

If a participant subsequently becomes pregnant while on study and continued study participation is permitted, the ICF(s) should include information indicating if breastfeeding is permissible or if replacement feeding (e.g., formula-feeding) is required.

4.6. Additional Regulatory, Policy, and Miscellaneous IC document Requirements and Considerations

All informed consent documents must meet U.S. regulatory informed consent requirements, ICH E6 (R2), relevant NIH and DAIDS policies and guidance, as well as any local, state, and/or national regulations, guidance, and institutional policies. The more stringent law, regulation, guidance, and/or policy(ies) applies. Additional regulatory, policy, and miscellaneous considerations include:

4.6.1. U.S. Certificates of Confidentiality

Certificates of Confidentiality (CoC) are used to protect the privacy of research participants by protecting investigators and institutions from being compelled to disclose identifying information that could have adverse consequences for participants. Certificates of Confidentiality can be used for biomedical, behavioral, clinical, or other types of research that are considered to be collecting or using identifiable sensitive information, e.g., research activities that include collecting genetic information, information on the psychological well-being of participants, data on substance abuse or other illegal high-risk behaviors. **Note:** all NIAID (DAIDS) supported research involving human participants or using individually identifiable biospecimens are subject to the NIH Policy for Issuing Certificates of Confidentiality and are automatically issued a CoC through a term and condition of award.

If the research is covered under a Certificate of Confidentiality, participants should be informed in the IC form of the use and limits of the certificate.

**NOTE:** Certificates of Confidentiality are issued for applicable research regardless of the country where the investigator or the protected information resides but they may not be effective for data held in foreign countries. If data from the research are collected in a country outside of the U.S. but these data are sent and maintained in the U.S., the certificate would be in effect (these data would be protected by the CoC from legal demand by the U.S legal system). In this instance, CoC-related language should be included in IC documents.

**SEE:**

- [Certificates of Confidentiality (CoC); General Information on Certificates](#);
- [Notice of Changes to NIH Policy for Issuing Certificates of Confidentiality](#);
- [Suggested Consent Language Describing the CoC Protections](#)
4.6.2. U.S. ClinicalTrials.gov Considerations

ClinicalTrials.gov is the trial registry databank maintained by the NIH National Library of Medicine (NLM). This databank was created to meet section 801 of the 2007 U.S. Food and Drug Administration (FDA) Amendments Act, known as FDAAA 801, that requires clinical trial registration and results submission for applicable clinical trials under this statute. Through FDAAA, the FDA modified the informed consent regulations at 21 CFR 50.25 to require that all IC documents for applicable drug and device clinical trials include a specific statement about trial registration into ClinicalTrials.gov. The Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11), which was released in September 2016, clarified and expanded the FDAAA 801 requirements.

**SEE:**
- [FDAAA 801 and the Final Rule; Which Trials Must Be Registered on ClinicalTrials.gov?](#)
- See also section 4.6.9 for the related NIH policy - [NIH Policy on Dissemination of NIH-Funded Clinical Trial Information (2017)](#)

For applicable clinical trials, the following language MUST be included verbatim in informed consent forms:

“**A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.**”

If the inclusion of the ClinicalTrials.gov-related language is mandated to be included in IC forms by the reviewing IRB/EC/RE for non-applicable trials, the FDA-required language may be modified as necessary.

**SEE:**
- The [Protocol Registration Manual](#) for detailed instructions;
- [21 CFR 50.25(c); FDA Guidance 2/2012: Guidance for Sponsors, Investigators, and Institutional Review Boards, Questions and Answers on Informed Consent Elements, 21 CFR § 50.25(c)](#)

4.6.3. European General Data Protection Regulation (GDPR)

The European General Data Protection Regulation (GDPR) [EU 2016/679)] went into effect on May 25, 2018. This regulation was enacted to protect the personal data of European Union (EU) citizens and includes anyone who can be identified directly or indirectly in a file or database (e.g., databases that contain a person’s name or an ID). U.S. federally funded human subjects research conducted in the EU, or is otherwise subject to EU regulations, is affected. IC documents, especially those used for obtaining consent for the use of participant data, need to address the requirements contained in the GDPR. To briefly summarize:

- Participants ages 16 and older, must be consented for the use (processing) of their personal data. Parental or guardian consent is required for those participants under age 16.
• Consent must be “presented in a manner which is clearly distinguishable from the other matters, in an intelligible and easily accessible form, using clear and plain language”.

• Participant have the right to withdraw consent at any time and must be informed of this right prior to giving consent.


4.6.4. U.S. Genetic Information Nondiscrimination Act (GINA)

GINA is a U.S. Federal law that prohibits discrimination in health coverage and employment based on genetic information. Consider the protections provided by GINA when developing informed consent processes and IC forms for genetic research, especially the impact of GINA on the risks and confidentiality protections for such research.

When applicable, ensure that GINA-related informed consent language accurately describes these protections.

NOTE: GINA protections are only effective in the U.S.

4.6.5. U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA Privacy Rule)

The 1996 U.S. Privacy Rule provides regulations pertaining to individually identifiable health and research information, otherwise referred to as “protected health information” or PHI. The Privacy Rule applies to certain U.S. health care providers and institutions that meet the requirements of a “covered entity”. A Privacy Board oversees the covered entities’ use and disclosure of PHI.

Often, the IRB/EC serves as the Privacy Board and includes HIPAA-related language in the IC form. HIPAA-related language can be combined with, or is in addition to, the basic and additional elements of informed consent, as found in the HHS regulation at 45 CFR 46.116(a) and (b).

NOTE: The HIPAA Privacy Rule is only effective in the U.S. It is up to the CRS to determine if this rule is applicable at their site, and up to the Privacy Board for a covered entity to determine when obtaining HIPAA authorization is necessary.
SEE: 45 CFR Parts 160, 162, and 164

4.6.6. International Committee of Medical Journal Editors (ICMJE) Requirements

Effective July 1, 2018, reports from clinical trials submitted to ICMJE member journals must contain “a data-sharing statement”. Trials that begin enrolling participants on or after January 1, 2019, must include a data-sharing plan at the time of trial registration on ClinicalTrials.gov or the WHO International Clinical Trials Registry Platform.

SEE: The ICMJE’s clinical trial registration policy

Informed consent considerations may include (if applicable):
• Informing participants that their de-identified data may be shared with future investigators, as well as the conditions under which their data may be shared (e.g., who may have access to their data and how, where their data may be stored)

• Informing participants about any data-sharing related risks such as risks to their privacy and confidentiality, and how these risks may be mitigated.

4.6.7. U.S. NIH Data-Sharing Policy

The 2003 NIH data sharing policy applies to those applicants seeking NIH funding of $500,000 or more in direct costs in any one year. This policy was established to ensure that data from NIH-funded research are shared as widely and freely as possible so that future research can build on previous efforts and discoveries, while safeguarding the privacy of participants and protecting confidential and proprietary data. The policy expects final research data, especially unique data, be made available to other investigators. Information should be included in the IC form about any steps that will be taken to minimize the risk of unauthorized disclosure of personal identifiers and participant re-identification, e.g., removing identifiers, withholding part of the data, and entering into data-sharing agreements.

See NIH Data Sharing Policy and Implementation Guidance (Updated: March 5, 2003)

4.6.8. U.S. NIH Genomic Data-Sharing (GDS) Policy

The 2014 GDS policy applies to the all NIH-funded research generating large-scale human or non-human genomic data and the use of these data for subsequent research. According to this policy, investigators who plan to use research or clinical samples or cell lines to generate genomic data may only do so if the participant has provided consent, even if these data are generated from samples that are de-identified. For research that meets the GDS policy (research that plans for “more complete” genetic testing, e.g., GWAS, rather than “limited” genetic testing such as HLA testing, etc.), IC documents should be reviewed to determine if it is appropriate for these data to be shared for secondary research use. NIH strongly encourages investigators to obtain consent that meets the GDS policy informed consent requirements as described below.

Convey the following information in language understandable to participants:

• Broad sharing: Participant’s genomic and phenotypic data and any other relevant data (e.g., disease status) may be used for future research purposes on any topic and shared broadly. If a participant does not consent to broad sharing of data, he or she may still be enrolled in the initial study, but the data may not be shared for future research.

• Databases: Data will be submitted to an NIH-designated data repository (e.g., dbGaP) after personal identifiers such as name, address, account and other identification numbers have been removed.

• Access: De-identified participant-level data may only be accessed in a controlled environment, unless participants explicitly consent to allow unrestricted access to and use of their data for any purpose.

• Re-identification: It may be possible to re-identify de-identified genomic data, even if access to data is controlled and data security standards are met, so confidentiality cannot be
guaranteed. Risks may include potential discrimination or stigmatization against participants, their families, or groups. There may also be unknown risks.

- Early Study Discontinuation: Participants may withdraw consent for research use of their genomic or phenotypic data at any time. However, data already distributed for research use will not be able to be retrieved.

- Secondary Research: Participants should be informed that no direct benefits should be expected from any secondary research use.

- Study Information: Participants should be provided with the name and contact information of an individual who is familiar with the research, will be available to address participant questions, and who is affiliated with the institution.

**SEE:** NIH Guidance on Consent for Future Research Use and Broad Sharing of Human Genomic and Phenotypic Data Subject to the NIH Genomic Data Sharing Policy

4.6.9. U.S. NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

The 2017 NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information requires registration and submission of results information in ClinicalTrials.gov, like that required by FDAAA (e.g., summary results, including adverse event information), for every NIH-funded clinical trial, including NIH-funded Phase 1 trials, trials of behavioral interventions and other non-FDA regulated products, regardless of whether they are subject to the FDAAA 801. This Policy is complementary to the statutory mandate under FDAAA (**SEE:** Section 4.5.2). IC documents for clinical trials subject to this NIH policy need to include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov. (**SEE:** Section 4.6.2).

- If the clinical trial is only subject to this NIH policy, the FDAAA informed consent language may be used. However, the phrase “as required by U.S. law” should be omitted.

- If the clinical trial is also subject to FDAAA 801 or the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11), then the FDAAA-required informed consent language must be included verbatim in the IC documents (**SEE** section 4.6.2).

**SEE:** NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

4.6.10. Post-Trial Access Considerations

Many Division of AIDS (DAIDS)-sponsored studies provide antiretrovirals and other study product(s)/intervention(s), both investigational and FDA-approved, to study participants during the conduct of the study. The Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) guidelines emphasize the importance of post-trial access. DAIDS recognizes the importance of study participants having access to beneficial interventions in relevant circumstances at the conclusion of a study. This post-trial access is especially relevant after efficacy trials when one or more products are proven effective. However, NIH’s Congressional mandate to “encourage and support research” (42 USC 284(b)(1)(A)) does not allow DAIDS to directly fund post-trial access to effective interventions, or any treatment.
Predicting and managing study product(s)/intervention(s) availability depends on multiple factors. During study planning, it is appropriate for investigators to discuss post-trial access by engaging with host countries’ authorities, pharmaceutical partners and other relevant stakeholders with the aim of facilitating post-trial access where appropriate.

When relevant, language related to post-trial access, including any referral to standard care, should be included in the ICF(s). This language may also include informing participants that the study can no longer provide the study product(s)/intervention(s) after participants complete their participation in a DAIDS-sponsored trial.

The current DAIDS General Use SIC Instructions and Template provides sample language for the ICF(s), addressing post-trial access ([Protocol Templates: Informed Consent Documents](#)).

“What happens at the end of this study?” section of the ICF template:

- Add information on the study product/intervention/interaction availability when the study is completed. If applicable, explain any plans for long-term followup, (e.g., tests, procedures, exams, etc.).

- Add the following for studies providing a drug, agent or device, and edit the language as appropriate. Include specific information related to any post-trial access programs or research studies providing drugs that may not be available locally:

  “Once you finish this study, researchers cannot give you ___ (insert drugs/agents, etc.). If ____ (insert drugs/agents, etc.) is helping you, the study staff may be able to tell you how to get it. But, it could be that you can only get something similar”.

4.6.11. Stored Samples and Associated Data Considerations

Human samples and associated data are an invaluable resource for current and future research on human health and disease. Protocol teams need to consider the technical aspects as well as the ethical, social, and regulatory issues surrounding the collection, storage, and use of samples and associated data.

Consider the following for inclusion in ICF documents, as applicable:

- Type of sample(s) to be used/collected/stored (e.g., vaginal secretions, blood, etc.)

- Collection of additional samples, if any, to be stored for future use

- How samples and/or associated data will be used in the current and/or future study(ies)

- Disposition of samples at the study’s completion (destroyed versus stored for future use)

- Length of time of storage (i.e., indefinite versus a finite specified length of time)

- Description of any planned genetic testing in the current and/or future research (i.e., limited versus broad genetic testing), development of cell lines, future research on HIV and related diseases, etc., and any associated risks

- Mandatory versus voluntary storage of leftover samples after the study’s completion
• Location of where samples may be stored, or whether samples will be shipped and/or stored outside of the country where they were collected

• Possibility of being re-contacted for the use of samples for future research not described in the IC form

• Discussion of GWAS, more complete genomic testing, NIH-designated genomic repositories (e.g., dbGaP), and other related issues for those studies that meet the NIH Genomic Data Sharing Policy (SEE section 4.6.8).

NOTE: Some ICF considerations are based on whether stored samples will only be used for the current study and/or for future research.

• Protocol batched testing: For protocols that will only store biological samples for batched testing for the current study and/or will not store samples for future research, the ICF(s) should address the issue of samples disposition at the study’s conclusion (e.g., all samples will be destroyed).

• Future research: For protocols that plan to use/store/collect biological samples (including leftover samples) and/or participant’s associated health data for future research, DAIDS strongly recommends the development of a separate ICF.

SEE:
• OHRP Guidance: Issues to Consider in the Research Use of Stored Data or Tissues;
• OHRP Guidance: Coded Private Information or Biological Specimens Use in Research;
• NIH Genomic Data Sharing Policy;
• NIH Website for the database of Genotypes and Phenotypes (dbGaP);
• DAIDS Sample Informed Consent Template for Stored Samples for Future Use

4.6.12. Incidental Findings (IFs) Considerations

An incidental finding (IF) is a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study. Protocols and ICF(s) should include any relevant information related to incidental findings, if applicable, including:

• The information to be offered back to participants

• The description of the approach to be used regarding the return of IFs to participants

• The type of IFs to be shared with participants:
  • All incidental findings, regardless of their importance, or
  • Only IFs that are important and actionable (at the site/CRS level), or
  • None

• If and how participants are to be re-contacted
4.6.13. Individual Research Results (IRRs) Considerations

In contrast to an IF, an individual research result (IRR) is a finding about a participant discovered during research on the focal variables under study in meeting the study’s aims. (Return of Individual Research Results & Incidental Findings: Facing the Challenges of Translational Science).

However, for practical purposes of research implementation, IFs and IRRs may be indistinguishable from each other. For example, in a research study to determine some genetic predispositions, some other associated predispositions may also be listed in the laboratory report, which are part of the study objectives. Thus, the genetic predispositions with clinical significance that are part of the research question would be IRRs, and the other associated predispositions that may also have clinical significance would be IFs. However, from the point of view of what to do with the information, the study team and the CRSs may decide to implement an approach to address both IRRs and IFs together without differentiating their separate origins. As such, protocols and ICF(s) should include relevant information on IRRs, similar to the IFs considerations described above.

NOTE: Both DAIDS IC templates (Protocol Specific IC form, and the Future Research Use of Stored Samples and Associated Health Information IC form) ask HIV research participants for their permission to be re-contacted for IFs that are both important for their health and actionable at the participant’s level, a variation of the approach above.

SEE:
- NIH Frequently Asked Question from Applicants-- Incidental Findings;
- NIH Genomic Data Sharing (GDS) Policy;
- DAIDS Sample Informed Consent Template for Stored Samples for Future Use and Instructions; DAIDS Protocol Specific Informed Consent Template — General Use and Instructions

5. GUIDANCE FOR SITE-SPECIFIC INFORMED CONSENT DOCUMENTS

Include in the site-specific ICF(s) essential information necessary for a potential participant to make an informed decision about study participation. Use culturally appropriate local “lay language”, and a language level and language understandable to the participant being consented. Information in site-specific ICF(s) need to be from the local perspective.

5.1. Site-specific ICF(s)

SSICFs must reflect awareness of and compliance with the following:

- U.S. regulatory informed consent element requirements, including compliance with 45 CFR 46.116 and 21 CFR 50.25 for research conducted under an IND and/or IDE (i.e., incorporating all the basic and additional elements of informed consent as appropriate)
• ICH E6 (R2) Informed Consent requirements, section 4.8, “Informed Consent of Trial Subjects”

• Relevant DAIDS policies and guidance directing aspects of ICF development and implementation (e.g., Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements, Protocol Registration) Division of AIDS Clinical Research Policies and Standard Procedures Documents.

• All applicable laws, regulations, guidance, and institutional policies at each clinical research site as well as any applicable NIH, NIAID, and DAIDS policies.

5.2. Additional Regulations and NIH Policies

There are additional regulations and NIH policies related to informed consent form development considerations include:

• Site-specific ICF(s) must include verbatim the FDA-mandated ClinicalTrials.gov language for applicable clinical trials (21 CFR 50.25(c)). If the reviewing IRB/EC/RE requires ClinicalTrials.gov-related language to be included in the site’s ICF(s) for non-applicable trials, the FDA-required language may be modified as necessary.


• Site-specific ICF(s) must include language pertaining to Certificates of Confidentiality for applicable research conducted at U.S sites (research protocols that will be collecting personally identifiable, sensitive information). Additionally, if data from the research are collected outside of the U.S. but these data are sent and maintained in the U.S., the site-specific should include related language.

  SEE: section 4.6.1 and Certificates of Confidentiality (CoC).

• Site-specific ICF(s) at U.S clinical research sites need to describe Genetic Information Nondiscrimination Act (GINA)-related protections, if applicable.


• Site-specific ICF(s) should include relevant local level information pertaining to the NIH Genomic Data Sharing (GDS), for studies meeting the GDS policy requirements

  SEE: section 4.6.8 and the NIH Genomic Data Sharing Policy.

• Site-specific ICF(s) need to include relevant information about Clinical Trials Insurance, if applicable (SEE: Section 4.3.6). A site can adopt/revise the following language, as appropriate, for their site-specific ICF(s):

  “Consistent with in-country guidelines (add as appropriate: regulations, laws, institutional policies, etc.), our clinic has purchased insurance to cover your medical treatment for study-related physical injuries that you are experiencing from participating in this study. We can also provide compensation for (add/clarify as appropriate: type of non-physical research-related injury compensation coverage provided by the site’s policy, e.g.,
psychological such as emotional distress, social such as family discrimination, financial such as lost wages, etc.”

5.3. IRB/EC/RE Considerations

- Site-specific ICF(s) must accurately reflect the information content of the protocol document, protocol ICF(s), and applicable protocol appendices, e.g., Schedule of Procedures.

**NOTE:** If the IRB/EC/RE requires any substantive changes or deletions of the informational contents of the protocol-specific ICF(s), the CRS may need to provide written documentation at the time of protocol registration, if applicable

**SEE:** The Protocol Registration Manual and Protocol Registration Policy

- Site-specific ICF(s), including English and/or local language versions (as applicable) as well as the protocol ICF(s) must be submitted for review and approval by the reviewing IRB/EC/RE and the DAIDS Protocol Registration Office (PRO), if applicable, prior to implementation at the clinical research site.

- English and local language versions of the same site-specific ICF(s) (e.g., enrollment ICF) must include the same information content.

- Language/wording used in site-specific ICF(s) does not need to match verbatim to the language used in the protocol-specific sample ICF(s) as long as the information content is the same; the focus is on mandated concepts rather than on mandated language.

**NOTE:** Information content from the protocol sample ICF(s) is not required to be in a specific section of the site-specific ICF(s) as long as this content is contained somewhere in the site-specific ICF(s).

- Reviewing IRBs/ECs/REs may determine that additional ICF(s) for a particular study are needed at the clinical research site as well as generic screening protocols/ICFs (e.g., screening, study participation, future use of samples and associated health information, written assent, etc.).

- Developing a separate site-specific ICF is strongly recommended if biological samples (including leftover samples) and/or participant’s associated health information will be collected and stored for future research.

**SEE:** Stored Samples and Associated Data Considerations, section 4.6.11

5.4. Key Concepts/Issues

There are some key concepts/issues that should be addressed at the local/site level, if applicable:

- Reasonably foreseeable risks, including those risks associated with the study intervention(s)/product(s)/strategy(ies), study procedures, social impact events, study participation, and any risks to a developing fetus (reproductive risks) and/or breastfeeding infant. The risk information in the site-specific ICF(s) should reflect the risk information included in the protocol and protocol-specific sample ICF(s).
NOTE: Reviewing IRBs/ECs/REs can require that site-specific ICF(s) include additional risk information than what is included in the protocol sample informed consent. Also, risk information in the protocol sample ICF(s) does not need to be included verbatim in the site-specific ICF(s) as long as the content is the same.

- Reasonably foreseeable direct and ancillary benefits at the site level, if any.
- Breastfeeding/replacement feeding requirements and related issues at the site level (e.g., availability of clean water).
- Disposition of biological samples at the study’s completion at the local level (e.g., destroyed versus stored locally or shipped outside of the country).
- Information related to incidental findings (IFs), if applicable. The following issues should be addressed if IFs will be disclosed to participants: (1) the possibility of discovering IFs; (2) participant’s choice to receive IFs; (3) participant’s permission to be re-contacted regarding IFs; and (4) if there is actionability at the site level for those IFs deemed to be clinically relevant and important. (SEE: Section 4.6.12).
- Individual Research Results (IRRs) considerations. (SEE: Section 4.6.13)
- Research-related injury issues at the local level, including the availability of treatment and compensation for injury.
- Information related to any referral to care and/or provision of care at the site level (e.g., treatment of STIs and provision of contraception/condoms).
- Post-trial availability of a study product/intervention at the site level
- Reimbursement for study participation at the local level as determined by the reviewing IRB/EC (e.g., time, effort, transportation).

NOTE: Reimbursement is not the same as compensation for research-related injury.

- Social impact events (e.g., inadvertent disclosure of study participation resulting in stigmatization or discrimination) that may be affected by local issues (e.g., anti-gay laws) should be described in the site-specific ICF(s), as applicable.

6. THE INFORMED CONSENT PROCESS
The informed consent process is a process by which a participant voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the trial that are relevant to the participant’s decision to participate. (ICH E6 (R2))

6.1. Recruitment
The consent process starts with the participant recruitment. Any study specific materials used for recruitment, such as posters or brochures or flyers, presenting the research study to the prospective participant must reviewed and approved by the appropriate IRB/EC/Regulatory Entity approval(s) prior to use.

6.2. Eligibility
Each study’s protocol has inclusion/exclusion criteria to determine who can or cannot participate in the study. These criteria describe characteristics that must be shared by all participants, e.g., age, gender, medical history, and current health status.

Enrolling participants with similar characteristics guarantees that the data from the study be related to the scientific question and not due to random factors. These criteria also make certain that people who could be made worse by participating in the study are not exposed to the risk.

Eligibility can be established by stand-alone screening consent process versus full study ICF process:

- In the stand-alone screening approach, potential participants are asked to provide private identifiable information and/or to submit themselves to various tests, for example laboratory tests, biopsies, etc. that would determine if they meet study specific inclusion/exclusion criteria and thus be eligible to enroll in the study. If they are found to be eligible for the study, candidates would then be offered a separate study specific ICF to be enrolled in the study.

- In the full study ICF process, potential participants give their consent to enroll in the study prior to being asked any specific inclusion/exclusion information or tests that are used to determine specific study eligibility, and thus remain or discontinue study participation.

6.3. Ongoing Consent Process

Obtaining a signature on an ICF does not complete the consent process. Maintaining informed consent requires that participants be provided with any new information and/or substantive change in the conditions or study procedures that arises during the course of the study (such as changes in risk, benefit, etc.) that may affect the participant’s decision to continue participation in the study. Participants should be provided with this information in a timely manner. As such, the informed consent process is ongoing throughout the entire research study until the participant decides to end his/her participation or until the study closes.

6.4. Study Closure

Once the study has concluded, as part of the ongoing consent process, participants should be notified of aggregated findings that may or may not impact each individual participant. Furthermore, if these findings result in changes to standard of care for the condition under study, alternative treatments and/or post-trial access information should be provided to all participants.

NOTES:

- Once a participant is enrolled in the study, the informed consent process continues with the research staff providing information regarding the study. The informed consent form is then presented and used as a guide for the verbal explanation of the study. The informed consent form must not serve as a substitute for discussion.

- It is important to the informed consent process that the research staff not only answer questions but also ask questions. Asking questions can further the discussion, initiate any questions from the potential participant, and help the research staff decide whether the person is truly understanding the study. However, research staff must be careful not to ask “trick” questions to test a participant’s
understanding, but rather ask direct questions with unique answers that can be easily recalled by the participant.

- In addition, it is important that the participant be given enough time and opportunity to review all possible options before signing the informed consent. The participant’s/LAR’s/parent(s)’s signature or mark provides documentation of agreement to participate in a study. Study-specific procedures cannot be conducted prior to obtaining research consent through an ICF(s) e.g., procedures done to verified study eligibility, directions to stop standard of care prior to study enrollment.

6.5. DAIDS Informed Consent Process Requirements

DAIDS permits the delegation of the task/responsibility of conducting the informed consent process discussion and obtaining informed consent, if this practice is permissible as per applicable local laws, regulations, guidance, and institutional policies, since the delegation of this task/responsibility is allowable as per HHS and FDA regulations. However, as is the case with any delegation of duties, staff conducting informed consent processes need to be “qualified” by education, experience, training, as well as knowledge of the study. Furthermore, when this task/responsibility is delegated, the investigator still retains the overall responsibility for the conduct of the study at the site, including this and any other delegated tasks/responsibilities.

SEE: DAIDS Delegation of Duties (Delegation of Responsibilities/Authorities) Log-Policy (in draft).

NOTE: Consult your local, state, and/or national regulations, guidance, and institutional policies regarding the delegation of obtaining informed consent. Follow the strictest of these regulations, as applicable.

To ensure that DAIDS supported and/or sponsored clinical research complies with HHS, FDA regulations as well as ICH E6 (R2) process standards, DAIDS requires all CRSs to have the following in place:

6.5.1. Informed Consent Process SOP and Documentation

All active sites conducting DAIDS sponsored and/or supported research must develop and implement an Informed Consent Process SOP. This SOP must include the following:

- Information about applicable local laws, regulations, guidance, and institutional policies pertaining to the informed consent process, including information related to delegating the task/responsibility of obtaining and documenting informed consent. The most stringent approach applies at the site level.

NOTE: A weblink, appendix, reference, and/or description in the SOP is acceptable.

- Information related to obtaining and documenting informed consent when vulnerable (e.g., children, prisoners, pregnant women, fetuses, neonates, decisionally impaired persons, etc.) and illiterate populations are participants (SEE: section 6.6).

- Information about who can serve as an impartial witness, when appropriate, based on local laws, regulations, guidance, and institutional policies.
• Relevant information about the investigator’s availability/involvement in the informed consent process, and how the investigator will supervise staff to whom trial-related duties such as obtaining informed consent (ICH E6 R2 section 4.2.5).

Clearly document the IC process in the participant’s research record. Documentation includes but is not limited to:

• Indicating the investigator's availability/involvement during the IC process (e.g., investigator was available to answer participant questions)
• Specifying the staff involved during the informed consent discussion (e.g., impartial witness, interpreter, study coordinator, etc.)
• Signifying that this IC process preceded study procedures, participant’s questions were answered, etc.

6.5.2. FDA Form 1572/DAIDS IoR Form – Delegation of Duties Including Informed Consent

In accordance with the DAIDS Protocol Registration Manual and Policy, site personnel who are responsible for making a “direct and significant contribution to the data” need to be listed on the FDA Form 1572/DAIDS IoR Form. Sites should include listing staff on these forms who have a significant role in conducting the informed consent discussion and obtaining informed consent.

The investigator ultimately makes the decision of who to list on the FDA Form 1572/DAIDS IoR Form, taking into account staff who routinely perform significant part(s) of the informed consent process. For example, the person providing the ICF document but who is not part of the discussion would be considered as having an insignificant role in the process. However, the person who performs the bulk of the informed consent discussion and/or any assessment of understanding of the discussion, and the person signing the ICF form would be considered as having a significant level of responsibility in the informed consent process and should be listed on the 1572 and IoR forms.

SEE: The Protocol Registration Manual for additional information on completing the FDA Form 1572/DAIDS IoR Form at: DAIDS Protocol Registration Manual

6.5.3. Document Maintenance

• Maintain the IC process SOP and study-specific DoD Logs as well as any relevant documentation, such as applicable local laws and guidance references and training documentation, in the site’s essential documents/regulatory binder/files. Please note that DAIDS does not require the IC process SOP or DoD Logs to be submitted to OCSO or to the Protocol Registration Office.

• Keep relevant correspondence (e.g., from the IRB/EC/RE, DAIDS, etc.) in the site’s essential documents/regulatory binder/files.

• Retain previous versions of all Informed Consent Process SOPs and DoD Logs in the site’s essential documents/regulatory binder/files.

SEE:

CTU PIs/CRS Leaders/ Principal Investigators are responsible for verifying that informed consent Quality Assurance (QA)/Quality Control (QC) checks are part of the site’s overall Clinical Quality Management Plan, as currently required by the DAIDS Requirements for Clinical Quality Management Plans policy. As a best practice, site staff delegated to conduct and oversee the consent process should always review and re-review IC documents to ensure that all required dates, entries and signatures are recorded prior to participant departure from the clinic.

SEE: Policy: Requirements for Clinical Quality Management Plans

6.6. Notifying Participants of New Findings or Changes to the Study

Circumstances may arise when it is necessary to revise ICF(s) to include important new information and/or changes to the study that are relevant for potential participants, as well as for those who are already-enrolled. These circumstances can include:

- New findings that change the risk/benefit profile (e.g., an unexpected adverse event or an adverse event occurring at greater frequency or severity than previously stated during the consent process);
- Procedures have been added, modified, or removed;
- New alternative treatments become available; and/or
- General study amendments.

Site-initiated revisions can also be made to site-specific ICF(s) due to: IRB/EC/RE stipulations; administrative changes (i.e., contact information), changes made to clarify ICF content, etc. The revised IRB/EC/RE-approved ICF(s) is/are then used to obtain participants consent to join or continue in the study.

These significant new findings and/or study changes may impact a participant’s willingness to join the study or to continue study participation. How participants are notified of these new findings or changes to the study may depend on the impact on study risk to participants and the immediacy needed to communicate the information.

While the study sponsor, protocol teams, and /or Investigators may suggest methods for disclosing information to participants, it is up to the IRB/EC/RE to ultimately determine the appropriate method for informing participants of any important new information and/or changes to the study.

NOTE: For already-enrolled participants, sponsors and IRBs/ECs/REs will determine if it is necessary to obtain the participant’s consent (i.e., re-consent) to the changes or new information
based upon the nature of the change in the research study and the new information that warranted the change.

6.6.1. New Findings

The HHS regulations at 45 CFR 46.116(b)(5) and the FDA regulations at 21 CFR 50.25(b)(5) state:

“A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.”

ICH E6 (R2), section 4.8.10(p) states:

“...that the subject or the subject’s legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject’s willingness to continue participation in the trial.”

However, the U.S. regulations and applicable guidance do not mandate a timeframe within which the new information will be provided to a participant. ICH E6 (R2) uses the phrase “timely manner” but does not quantify this term.

It is DAIDS expectation that when there are any changes made to ICF(s), these updated ICF(s) must be reviewed and approved by the IRB/EC/RE, as appropriate, and be implemented “immediately”, upon receipt of the IRB/EC/RE-approved ICF(s). This requirement applies to consenting new study participants as well as to re-consenting already-enrolled participants (when re-consent is mandated by the sponsor and/or IRBs/ECs/REs). In this context, “immediately” and “timely manner” is interpreted as “without delay”, usually by or at the participant’s next study visit.

NOTES:

• When appropriate, consent documents should include a statement that significant new findings will be provided to the participant. The U.S. regulations and guidance and ICH E6 (R2) (section 4.8.2) require that ICF(s) be revised whenever important new information becomes available that may be relevant to the participant’s consent.

• For already-enrolled participants, sponsors and IRBs/ECs/REs will determine if it is necessary to obtain the participant’s consent to the changes or new information based upon the nature of the change in the research study and the new information that warranted the change. This process is referred to as “re-consenting” the participant. When participants are re-consented, they need to be provided a signed and dated copy of the ICF (ICH E6 R2 4.8.11, and DAIDS Guidance on Reconsenting).

6.6.2. Study Amendments [Full Version Protocol Amendment or Letters of Amendment (LoA)]

Changes to the study are made through amendments that are submitted to and reviewed and approved by the IRB/EC/RE as applicable.

When required by the sponsor and/or IRB/EC/RE, communicate change(s) in study related information that may influence a participant’s decision to participate or continue his/her
participation in a study through the revised consent document. Any associated study changes are not to be implemented until after written re-consent is obtained from the participant.

Similar to obtaining initial informed consent, each participant is given sufficient time to read the new information and revised consent documents, and ask questions, before being asked to sign the revised IC. The participant’s signature is affirmation of his/her willingness to continue study participation.

6.6.3. DAIDS Dear Participant Letters or Participant Notifications

A DAIDS Dear Participant Letter is a letter, text, or other means of quickly disseminating written information which may be used to notify participants of planned actions or other new information. Depending on the nature of new information, this communication can be either “urgent” or “non-urgent”.

- Expedited Safety Notification or “Urgent” Dear Participant Letters

  This type of notification is used when there are significant and immediate participant safety concerns related to a study product/intervention/strategy; and sites, participants, investigators, and IRBs/ECs/REs must be notified in an expedited manner to ameliorate real and apparent immediate study-related harm. Plans to ameliorate the immediate potential for harm, including planned participant communication must be promptly sent to the IRB/EC/RE. Once the IRB/EC/RE notification is made, an amendment to the protocol and IC documents is submitted for IRB/EC/RE review and approval.

  While this mechanism does not require IRB/EC/RE approval prior to distribution, IRBs/ECs/REs must be promptly notified of any event that increases immediate risk of harm to participants. This initial notification to participants may be done verbally and may occur before an official and complete Dear Participant Letter is finalized. This verbal notification must be documented in the participant’s study records.

  NOTE: When the sponsor and/or IRB/EC/RE requires re-consent, Dear Participant Letters CANNOT be used in lieu of a complete informed consent form and process to document a participant’s agreement to continue study participation. If participants are asked to sign these letters to document receipt, their signatures DO NOT constitute any type of consent. Document in each participant’s research record that the participant was sent the Dear Participant Letter, and if applicable, that it was received.

- “Non-Urgent” Dear Participant Letters

  This type of notification can be used to convey non-urgent new information and/or changes to current or past study participants, such as aggregate study findings, study completion, etc. Since the intent of such letters is not to communicate information to eliminate apparent immediate harm, this type of Dear Participant letter requires IRB/EC/RE review and approval, as applicable, prior to distribution.

6.6.4. Addenda

Another means of conveying new information is the use of an addendum to the IC document. This method can be used to convey information that does not change the risk of harm to
participants but informs them of a change, e.g., the closure of a study arm, a change in visit schedule, etc. Each addendum must be approved by the IRB/EC/RE before it is provided to participants.

6.6.5. Scripts

Scripts are the written dialogs that are used to convey study specific information to participants. By reciting the same information, message consistency is maintained. This information must be IRB/EC/RE approved except when used to eliminate apparent immediate harm to study participants. Scripts may also be used, for example, when conducting study visits and to communicate visit reminders or adherence measures and HIV counseling.

Some important tips to remember when writing this type of script are:

- Create scripts that are engaging and motivate a conversation rather than being instructive in nature
- Refer to yourself as “I” and to the participant as “you”
- Write the script as if you were speaking
- Rehearse the script by yourself, or talking to a friend, the oral script presentation prior doing with real participants

**NOTE:** the use of Scripts for consenting potential participants who cannot read or write in any language, or who have only basic levels of education, may be a beneficial tool.

6.7. Vulnerable Populations

Vulnerable populations may be considered as potential research participants if adequate provisions are established. When some or all of the research participants are likely to be vulnerable to coercion or undue influence, additional specific safeguards to protect the rights and welfare of these participants must be included in the study and informed consent process as per HHS and FDA regulations and ICH E6 (R2). Vulnerable participants may include children, prisoners, fetuses, neonates, decisionally impaired persons, ethnic minority groups, members of a group with a hierarchical structure, persons with incurable diseases, persons in nursing homes, refugees, persons in emergency situations, and the economically or educationally disadvantaged.

The Council for International Organizations of Medical Sciences (CIOMS) Guidance addresses the vulnerable populations issue from a more general perspective. CIOMS states: “Sponsors, researchers, governmental authorities, research ethics committees and other stakeholders must ensure that the benefits and burdens of research are equitably distributed. Groups, communities and individuals invited to participate in research must be selected for scientific reasons and not because they are easy to recruit because of their compromised social or economic position or their ease of manipulation”. In addition, “... The equitable distribution of benefits and burdens in the selection of study populations requires that the benefits of research be distributed fairly and that no group or class of persons bears more than its fair share of the risks or burdens from research participation”.

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CIOMS guidelines call for investigators and sponsors to respect the autonomy of all research participants and to implement research that follows the principal of “Justice”. In this respect CIOMS states: “Justice requires also that the research be responsive to the health conditions or needs of vulnerable subjects. The subjects selected should be the least vulnerable necessary to accomplish the purposes of the research. Risk to vulnerable subjects is most easily justified when it arises from interventions or procedures that hold out for them the prospect of direct health-related benefit. Risk that does not hold out such prospect must be justified by the anticipated benefit to the population of which the individual research subject is representative”.

### SEE:

- The Council for International Organizations of Medical Sciences (CIOMS) International ethical guidelines for health-related research involving humans sections (3): Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research; (4): Individual informed consent; (13): Research involving vulnerable persons; (14): Research involving children; and (15): Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent;
- DAIDS: Clinical Trial Protocol Documents Manual, section 18.2;
- ICH E6 R2, sections 1.6.1 and 3.1.1

### 6.7.1. Children in Research

Children and adolescents can participate in research, unless there is a sound scientific justification for their exclusion. Due to their changing physical and emotional development, children may be at increased risk of harm when participating in research. In addition, their evolving capacity to consent may limit their ability to make fully informed decisions regarding participation. Thus, the HHS regulations at 45 CFR part 46 Subpart D and when applicable, 21 CFR 50 Subpart D, require additional safeguards and protections for children involved in research.

A child is a person who has 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 [45 CFR part 46.402(a) and 21 CFR part 50.3(o)]. Who is legally considered a child may vary from location to location. In addition, there may be some circumstances under which a minor would not meet the definition of a child and can therefore consent for themselves for clinical care and/or research, depending on the locale.

Children may participate in research if all of the applicable requirements at 45 CFR part 46 Subpart A and D (and 21 CFR 50 Subpart D for FDA-regulated research) are satisfied. Proposed research with children is permissible with IRB/EC approval under §46.404, 405 or 406 and §50.51, 52, and 53, when applicable. Research not otherwise approvable by the IRB/EC (§46.407 and §50.54), may be permissible after HHS-level review.

For all permissible categories of research with children, the IRB/EC is responsible for determining that adequate provisions are made for soliciting the assent of the children, soliciting the permission of each child’s parents or guardian-or one parent or guardian, as appropriate as per §46.408 and §50.55, when applicable (SEE: sections 6.3.1.1 and 6.3.1.2).
SEE:

- OHRP Research with Children FAQs;
- DAIDS Policy: Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements; Appendix 1-Risk/Benefit Categories; Appendix 2-Examples of Template Language; Appendix 3 Wards; and Appendix 4- Waivers of Parental/Guardian Permission or Child Assent
- DAIDS Policy: Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements; requires the clinical research site to submit the IRB’s/EC’s designation of a risk/benefit category and subsequent IRB/EC approval to DAIDS;
- DAIDS Clinical Trial Protocol Documents Manual, section 18.3.2;
- 45 CFR 46.408 - Requirements for permission by parents or guardians and for assent by children.;

6.7.1.1. Assent of a Minor

The IRB/EC may determine that children are capable of giving assent when children and adolescents are participating in the research. As per 45 CFR 46.402(b), “‘Assent’ means a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent”. As such, the child should be engaged in the research discussion, using age-appropriate information. The IRB/EC is responsible for determining if there are adequate provisions for obtaining child assent and parent/guardian permission.

IRBs/ECs should consider age, individual circumstances, life experiences, physical and emotional development, and the proposed research when deciding the need for assent. If an IRB/EC determines that assent is required, it also determines how assent must be documented. However, if the IRB/EC determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB/EC determines that the participants are capable of assenting, the IRB/EC may still waive the assent requirement under circumstances in which consent may be waived in accord with 45 CFR part 46.116 of Subpart A, and 21 CFR 50.55 for FDA-regulated research.

Even though the HHS regulations do not require documentation of assent, the IRB/EC may determine an appropriate method for documenting child assent. Based on all the considerations discussed above, adolescents research participants could also give consent using the adult form of the informed consent form, but parental permission would still be required. When the IRB/EC determines that written assent is not required, documentation of child’s verbal assent must be documented in the participant’s research record. The IRB/EC may also decide that the assent is not needed.

SEE:
6.7.1.2. Parental/Guardian Permission

In accordance with 45 CFR part 46.408 and 21 CFR 50.55 for FDA-regulated research, the IRB/EC determines that adequate provisions are made for soliciting the permission of each child’s parents or guardian. Where parental permission is to be obtained, the IRB/EC may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405 (or §50.51 or §50.52 for FDA-regulated research). Where research is approved under §46.406 and §46.407 (or §50.53 or §50.54 for FDA-regulated research) and permission is to be obtained from parents, both parents must give their permission 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. Permission by parents or guardians must be documented in accordance to the extent required by §46.117 (and §50.27 for FDA-regulated research).

In general, there are three categories of research with children that can be approved by IRBs/ECs, when:

- The risks of the research are no more than minimal.
- More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual participant or by a monitoring procedure that is likely to contribute to the participant’s well-being; the risk is justified by the anticipated benefit to the participants; and, the relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.
- More than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual participant, or by a monitoring procedure that is not likely to contribute to the wellbeing of the child; the risk represents a minor increase over minimal risk; the intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations; and, the intervention or procedure is likely to yield generalizable knowledge about the participants’ disorder or condition which is of vital importance for the understanding or amelioration of the participants’ disorder or condition.
For non-FDA regulated research, if the IRB/EC determines that parental or guardian permission is not a reasonable requirement to protect the child participant (e.g., neglected or abused children), it may waive the permission requirements and substitute an appropriate mechanism for protecting these participants, if the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism depends upon the nature and purpose of the procedures described in the protocol, the risk and anticipated benefit to the participant and his/her age, maturity, status, and condition.

Note: children that reach the legal age of consent during their study participation need to be asked to consent to their continued participation through a written informed consent form, unless the IRB/EC determines that the requirements for obtaining informed consent can be waived. Parental permission is no longer required for the now-adult participant.

**SEE:**
- 45 CFR 46, Subpart D; 21 CFR 50, Subpart D;
- ICH E6 R2 Section 4.8.12;
- DAIDS Policy: Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements; Appendix 1-Risk/Benefit Categories; Appendix 2-Examples of Template Language; Appendix 3 Wards; and Appendix 4- Waivers of Parental/Guardian Permission or Child Assent
- DAIDS Clinical Trial Protocol Documents Manual, section 18.3.2;
- OHRP Research with Children FAQs: Research Involving Children NIH Policy Requirements for the Inclusion of Children in Research CIOMS Guideline 17

### 6.7.1.3. Wards

The HHS regulations at 45 CFR part 46, subpart D and 21 CFR 50, subpart D for FDA-regulated research, provide additional protections for children who are also wards of the State or any other or entity. If the research is approved under §46.406 or §46.407 (or §50.53 or §50.54), the regulations require that the IRB/EC appoint an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. The advocate agrees to act in the best interests of the child throughout the duration of the child’s participation in the research. In this instance, the advocate will observe or participate in the informed consent process and to the extent possible, ensure that the child understands what will be required of him or her during the research, and that if capable, the child provides his or her assent to participate.

**SEE:** 45 CFR 46.409 Wards; 21 CFR 50.56;

**OHRP Research with Children FAQs**

### 6.7.2. Pregnant Women, Fetuses, and Neonates in Research

Women of child-bearing potential can participate in research, unless there is a sound scientific justification for their exclusion. However, these women need to be informed about any
additional risks to themselves and/or their developing fetus. Furthermore, women should be informed about any other related risks, including any psychological, social, physical, or legal risks if they should decide to participate in the research (e.g., risk of physical harm if their significant other finds out about their research participation, etc.).

**SEE:** The “Additional Pregnancy-Related IC form Requirements and Other Considerations”, section 4.5

### 6.7.2.1. Pregnant Women and Fetuses

When the research holds out the prospect of direct benefit to the pregnant woman or to both the pregnant woman and the fetus, or there is no prospect of benefit for the woman or the fetus but the risk to the fetus is not greater than minimal risk and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, only the pregnant woman’s consent needs to be obtained in accordance with the informed consent provisions of 45 CFR 46 Subpart A and §46.204 (d).

When the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father are obtained in accordance with the informed consent provisions of 45 CFR part 46 Subpart A and §46.204 (e). However, the father's consent is not required if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest. 45 CFR 46.204(e).

As per §46.204(f), persons providing consent under §46.204 (d) or (e) must be fully informed of any reasonably foreseeable impact of the research on the fetus or neonate.

For children, as defined at §46.402(a) (and §50.3(o)), who are pregnant and are participating in research but cannot provide consent, assent and permission are obtained in accordance with 45 CFR part 46 Subpart D (and 21 CFR 50 Subpart D, if applicable). However, if the research only involves treatments or procedures for which minors can give consent outside the research context (under applicable local/in-country laws, regulations, and guidance), such participants would not meet the regulatory definition of “children”. Under these circumstances, minors may be able to consent on their own behalf.

**SEE:**
- 45 CFR part 46 Subpart B. Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research;
- OHRP Research with Children FAQs;

**NOTE:** FDA regulations (21 CFR 50) do not include an equivalent section to 45 CFR 46 Subpart B.

### 6.7.2.2. Neonates

As per 45 CFR 46.205 viable neonates, neonates of uncertain viability, and nonviable neonates may be involved in research if certain conditions are met. §46.202(d) defines a “neonate” as a newborn infant. The World Health Organization qualifies this definition as “a child under 28 days
of age”. In addition, a “viable neonate” is a newborn that is, after delivery, able to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration (§46.202(h)).

For neonates of uncertain viability and nonviable neonates involved in research, each individual providing consent under §46.205 (b)(2) or (c)(5) must be fully informed regarding the reasonably foreseeable impact of the research on the neonate as per §46.205 (a)(2).

For neonates of uncertain viability, until it has been ascertained whether or not the neonate is viable, the neonate may not be involved in research covered by 45 CFR part 46 Subpart B unless the additional conditions at §46.205 (b) have been met. In this instance, it is necessary to obtain the legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent’s legally authorized representative (LAR) in accordance with 45 CFR part 46 Subpart A. If the pregnancy resulted from rape or incest, the consent of the father or his LAR is not necessary.

**SEE:** 45 CFR part 46,205(b)(2)

For neonates determined to be viable after delivery, they may be involved in research only to the extent permitted by and in accordance with the requirements of 45 CFR part 46 Subparts A and D (e.g., parental permission obtained). As per §46.202(b), “delivery” means complete separation of the fetus from the woman by expulsion or extraction or any other means” (§46.202(b)).

**SEE:** 45 CFR part 46 Subpart B. Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research; CIOMS Guideline 18 and 19

**NOTE:** FDA regulations (21 CFR 50) do not include an equivalent section to 45 CFR 46 Subpart B.

6.7.3. Prisoners in Research

As per §46.03 (c), a “prisoner” is “any individual involuntarily confined or detained in a penal institution”. This includes “individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing” (§46.303(c)).

Prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary or un-coerced decision about research participation (impact on their ability to provide informed consent). The HHS regulations at 45 CFR part 46, Subpart C require additional protections for prisoners who are involved as participants in research. IRBs/ECs reviewing research involving prisoners must comply with additional composition requirements and duties of the HHS regulations at 45 CFR part §46.304 & §46.305.

The risk of the participating in the research must be commensurate with risks that would be accepted by non-prisoner volunteers. (§46.305(3)).

OHRP details a set of procedures about what to do if a research participant becomes a prisoner during the study, even when this circumstance is not covered by the signed IC form:
• The PI should notify the IRB/EC immediately, and the prisoner should be temporarily withdrawn from the study until all of the requirements of 45 CFR 46 Subpart C have been met.

• In special circumstances in which the PI asserts that it is in the best interest of the now prisoner participant to remain in the study while incarcerated, the participant may continue to participate in the research until the requirements of 45 CFR 46 Subpart C are satisfied. However, the PI must promptly notify the IRB/EC of this occurrence, so the IRB/EC can re-review the study.

SEE:
- 45 CFR 46 Subpart C. Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects;
- DAIDS Clinical Trial Protocol Documents Manual section 18.2.2;
- OHRP’s Guidance - Prisoner Involvement in Research (2003);
- OHRP’s Prisoner FAQs

NOTE: FDA regulations (21 CFR 50) do not include an equivalent section to 45 CFR 46 Subpart C.

6.7.4. Diminished capacity/Impaired Consent Capacity/Decisionally Impaired Persons in Research

A wide variety of diseases, conditions, and injuries can affect an individual’s ability to weigh the advantages and disadvantages of participating in research, and to provide informed consent.

An IRB/EC/RE that reviews research involving individuals with diminished capacity/impaired consent capacity/decisionally impairment must include members who are knowledgeable about or experienced in working with such participants. Investigators may want to consider developing supplemental study specific informed consent materials, which should always be reviewed and approved by the appropriate IRB/EC. Furthermore, investigators should consider: assessing the consent capacity of potential participants using standardized testing aids; determining whether the IRB/EC or a third party should observe the consent process; considering additional monitoring; extending time periods for decision making; and/or re-assessing the participant’s decision-making capacity throughout the course of the research. Informed consent may be sought from a participant’s LAR as described throughout 45 CFR part 46.

Impaired consent capacity may involve partial impairment, impairment that changes over time, or complete impairment. If a participant’s consent capacity is sufficiently impaired that the participant is unable to provide legally effective informed consent, IRBs/ECs and investigators must consider whether or not a LAR can give consent/continued consent on behalf of the adult participant, if permitted by the laws of the jurisdiction in which the research is conducted.

SEE:
- NIH Research Involving Individuals with Questionable Capacity to Consent: Points to Consider; OHRP IC FAQ What should be considered in seeking informed consent from individuals with diminished decision-making capacity?
6.7.5. Local Language Speakers

The HHS and FDA regulations as well as ICH E6 (R2) (section 4.8.6) require that informed consent information be presented in a language understandable to the participant. Potential participants and, when applicable, their LAR, who do not speak/understand the most commonly used local language should be presented with a consent document written in a language understandable to them, i.e., in a language and at a level they can understand, using lay terms to describe scientific and medical terms. Potential participants should not be routinely excluded from participating due to language issues and barriers.

Alternatively, a presentation of the informed consent information in conjunction with a short form written consent document (stating that the HHS and FDA regulatory elements of consent have been presented orally) and an IRB/EC-approved written summary of what is presented orally may be used in lieu of a long form consent. An impartial witness to the entire oral presentation is required, and the participant is given a copy of the short form document and the summary. The oral presentation and the short form written document must be in a language understandable to the participant. The IRB/EC-approved long form IC document may serve as the summary. The witness must be fluent in both the language used in the long form consent as well as the short form consent (the language understood by the participant). When the person obtaining consent is assisted by an interpreter, the interpreter may serve as the witness; however, an interpreter who is also a witness must be not affiliated with the study. Additionally, participants must receive a copy of the long IC or the summary written in the most commonly used language at the site and a copy of the short form in the language understood by the participant (SEE: Sections 7.3 and 7.4).

When investigators can reasonably anticipate potential participants that may not speak/understand the most commonly used local language but can speak/understand less common local languages, they should submit to the IRB/EC appropriately translated consent documents in these anticipated languages (i.e., either a long form or a short form with written summary). IRBs/ECs should also be provided with a description of how interpreters will be made available during the informed consent process.

There may be occasions when investigators have not anticipated a potential participant who speaks/understands a less commonly used local language and, therefore, do not have an appropriate IRB/EC-approved written translation of the IC documents and summary. Some circumstances may allow sufficient time to prepare translated IC documents and receive IRB/EC approval prior to enrolling the participant. Other circumstances may not allow sufficient time. As per FDA guidance, a contingency for this situation could include translating a generic short form in multiple languages that satisfies the requirements of 21 CFR 50.27(b)(2), and obtain IRB/EC approval for using these generic short forms to enroll such participants.
6.7.6. Illiterate persons

A person who speaks and understands the language used for both the consent forms and during the consenting process, but does not read and write this language, can enroll in a study and consent to study participation. A modified informed consent process should be considered by the IRB/EC, including the use of a short form ICF, oral presentation of the information contained in the long form ICF, and a written summary.

Sites need to record in the research record the method used for communication with the prospective participant and the specific means by which the prospective participant communicated agreement to participate in the study. A third party must witness the entire consent process and sign the consent document. Although an impartial witness is not required by HHS regulations, an impartial witness is required by ICH E6 (R2) and DAIDS policy (SEE: section 7.3). As per ICH E6 (R2) section 4.8.9, “the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject’s legally acceptable representative, and that informed consent was freely given by the subject or the subject’s legally acceptable representative”. In addition, a video tape recording of the consent interview is recommended when consenting non-speakers and illiterate populations.

SEE:

- FDA A Guide to Informed Consent - Information Sheet Illiterate English-Speaking Subjects;
- Clinical Trial Protocol Documents Manual section 18.2.4;
- ICH E6 R2 section 4.8.9.
7. DOCUMENTATION OF INFORMED CONSENT

7.1. Legal signature/thumbprint/mark/electronic signature

The participant’s/LAR’s signature on the ICF documents signifies the participant’s willingness to participate in the study or the LAR’s consent on behalf of a potential participant. The person obtaining informed consent needs to ensure that the participant’s/LAR’s signature follows applicable law(s), reviewing IRB/EC/RE requirements, institutional policies, CRS SOPs, and the IRB/EC/RE-approved protocol. In general, the signature must be the individuals’ legal name, but participants can use any designation he/she wishes to adopt as a signature for the duration of the study, as long as there is no local law or institutional standards that allows it (traditional signature, a mark, thumb print, or other method of “making their mark” as long as it meets local law or institutional standards). The written signature must be in ink.

**SEE:** The Essential Documents Guidance, “Signature Documentation” section.

A participant/LAR who speaks and understands the language of the ICF, but does not read and write the language can give consent/permission to be in a study by “making his/her mark” or by fingerprint/thumbprint on the ICF, when this is consistent with applicable law(s), etc. In this situation, the participant’s research record should indicate the reason for the lack of a signature.

Traditionally, informed consent is obtained in a face-to-face interview using paper consent forms. It is permissible for an investigator to use an alternate method for the informed consent process, such as conducting the informed consent process through email, phone or video chat, and obtaining written informed consent or parental permission by facsimile, secure email, or eIC (electronic informed consent; **SEE:** Section 7.7). An investigator may obtain an electronic signature (e-signature) to document informed consent or parental permission, if e-signatures are legally valid within the local jurisdiction where the research is being conducted and the IRB/EC has approved this method to document informed consent. The investigator should be able to verify that the e-signature is legitimate. The CRS’s informed consent process SOP should include relevant information about this alternative process, as applicable. As per FDA guidance, an e-signature is considered to be the “legally binding equivalent of the individual’s handwritten signature” (§ 11.3(b)(7)).

In general, informed consent is documented by the use of an IRB/EC/RE-approved written ICF. The participant or LAR signs and dates the ICF and should receive a copy of the signed and dated written ICF as per ICH E6 (R2) (section 4.8.11).

**SEE:**
- 45 CFR 46.117(a)(c), 21 CFR 50.27 (a), 21 CFR 56.109(c); **ICH E6 R2** section 4.8.11;
- The Age and Identity Verification and Co-Enrollment Prevention Policy;
- **OHRP Informed Consent FAQs**;

7.2. Legally Authorized Representative (LAR)

As per the current version of 45 CFR 46 part 102 (c) and 21 CFR 50.3 (l), a LAR or “legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research”. ICH E6 (R2) has a similar definition for legally acceptable representative: “An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial”. Who can act as the legally authorized/acceptable representatives is determined by the laws of the jurisdiction in which the research is conducted (e.g., local/in-country laws and guidance, institutional policies, etc.). Legally authorized/acceptable representatives should consider the individual’s previous preferences and values, if applicable, and the degree that study participation is in the participant’s best clinical interest.

**NOTE:** The revised Common Rule, when implemented, expands the definition of a “legally authorized representative”.

**SEE:** Section 8.2.1, Expanded definition of LAR.

7.3. Impartial Witness

An impartial witness must be present to observe the consent process when obtaining consent participants who do not speak/understand the language used to write the long ICF (section 6.3.5), illiterate/low literacy potential participants (section 6.6.6) and whenever the short form ICF process is used (section 7.4). As per ICH E6 (R2), section 1.26, an impartial witness is “a person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject”. The purpose of the impartial witness is to corroborate the voluntariness of the participant’s/LAR’s consent and the adequacy of the consent process by ensuring that the information was accurately explained, and the participant’s/LAR’s questions were satisfactorily addressed. In order to fulfill this role, the impartial witness must be fluent in the language of the oral presentation.

The witness must be an impartial third party, not otherwise connected with the research (i.e., not involved in the design, conduct, or reporting of the research study). The witness may be a family member or friend, “participant advocate”, staff member not involved in the trial or who does not work directly for the investigator, or anyone who can act in the best interest of the participant. The witness must be present (physically or by some other means, such as phone or video conference) during the entire consent discussion.

A witness must be present when the participant/LAR is unable to read (e.g., illiterate, blind) and when the long ICF method is used and read to the participant or LAR. There must also be an impartial witness present when the short form ICF method is used (**SEE:** Section 7.4).
Under circumstances during which an interpreter is used during the informed consent discussion with the participant/LAR in the participant’s local language, the interpreter can also serve a dual role as the witness, if s/he is also an impartial third party to the research.

**SEE:**
- [ICH E6 (R2)](https://www.fda.gov/regulatory-information/search-federal-guidance-documents/ich-e6-r2) section 1.26; Sections 6.3.5, 6.3.6, and 7.4;
- [DAIDS Clinical Trial Protocol Documents Manual](https://www.aidsinfo.nih.gov/ContentFiles/DAIDSManual.pdf) sections 18.2.4 and 18.3.3

### 7.4. Short Form ICF/Informed Consent Summary/Long Form ICF

The regulations provide two different methods for obtaining written informed consent/parental permission:

- **Long form ICF:** The long form ICF includes all the elements of informed consent as required under the HHS and FDA (when applicable) regulations and is written in a language and at a reading level that is understandable to the participant/LAR. The participant/LAR and the person obtaining consent sign the long form ICF. When the long ICF is used, the person obtaining consent will provide a copy of the long ICF to the participant/LAR.

- **Short Form ICF:** The short form ICF states that the elements of informed consent as required under the HHS and FDA (when applicable) have been presented orally to the participant/LAR. A copy of the short form ICF and the written summary must be given to the participant/LAR. The participant/LAR must sign and date the short form. The witness must sign both the short form and the summary. The person obtaining consent/permission must sign the summary.

The IRB/EC will approve which method(s) the investigator can use to obtain written consent/permission. Unless the IRB/EC waives the requirement to 1) obtain informed consent or 2) obtain written informed consent, a written IC document in a language that is understandable to the participant must be used. The consent document used can be either the IRB/EC-approved short form (accompanied by the written summary) or the IRB/EC-approved long form, as long as the short form or long form informed consent has been translated into a language understandable by the participant.

If the participant/LAR cannot speak or read the language in the ICF, appropriate interpreter services need to be made available throughout the course of the research, since informed consent is a process that occurs throughout the course of the study. The interpreter may be a member of the research team, a family member, or friend of the participant/LAR. The person serving as the interpreter will interpret in the local language, the one understood by the participant, the consent document/written summary with the participant/LAR, explaining the study details in such a way that the participant/LAR understands the study, the required elements of informed consent, and his/her obligations as a participant part in the study.

In this instance, informed consent is documented using an IRB/EC-approved short form ICF that has been translated into a language understandable to the prospective participant/LAR. Additionally, the IRB/EC needs to approve a written summary of what is to be said to the
participant/LAR; the IRB/EC-approved long form ICF can be used as this written summary (SEE: Section 6.6.5).

### SEE:

- §46.116 and 117; §50.25 and 27;
- DAIDS Clinical Trial Protocol Documents Manual section 18.3.3
- OHRP Guidance: Informed Consent of Subjects Who Do Not Speak English

#### 7.5. Waiver and alteration of Some Elements of Informed Consent or Parental Permission for Non-FDA Regulated Studies

The HHS regulations at 45 CFR 46 allow an IRB/EC to waive the requirement for obtaining informed consent or parental permission, or to approve a consent procedure that leaves out or alters some or all of the elements of informed consent otherwise required under 45 CFR 46.116(a) and (b).

Waiving the requirement for obtaining informed consent or parental permission means that the IRB/EC has determined that investigators do not need to obtain the participant’s informed consent to participate in research. For example, some minimal risk, behavioral research in a clinic setting may require that participants be unaware that the research is taking place.

**SEE:** 45 CFR 46.116(c) and (d)

**NOTE:** FDA regulations do not contain an equivalent informed consent waiver process.

#### 7.6. Waiver of Documentation of Informed Consent or Parental Permission

The HHS and FDA regulations allow an IRB/EC to waive the requirement to obtain a signed consent form for some or all of the participants. In cases in which the documentation requirement is waived, the IRB/EC may require the investigator to provide the participants with a written informed consent form or statement regarding the research (e.g., information sheet, written ICF).

An IRB/EC may waive the requirement to obtain a signed consent form when either: “(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject’s wishes will govern; or (2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context”. In these cases, the IRB/EC may determine that either the participant’s oral consent or, in the case of online survey research, the participant’s consent is implied by the completion of the survey instrument.

During an informed consent process where the IRB/EC has waived the requirement to obtain a signed consent form, the investigator must provide the participant with all of the relevant information (e.g., review the eight basic elements of informed consent §46.116 and §50.25, if
applicable), answer the participant’s questions, and confirm that the participant understands the
information provided before obtaining the participant’s verbal consent. The individual obtaining
verbal consent must document the date that verbal consent was obtained and include a
statement of what information was provided to the participant (e.g., information sheet) in the
participant’s research record.

**NOTE:** The revised Common Rule, when implemented, has an additional requirement for the
IRB/EC approval of an informed consent documentation waiver request: “Where the participants are members of a cultural group in which signing forms is not a normal/acceptable practice.”

**SEE:**
- 45 CFR 46.117(c) and 21 CFR 56.109(c);
- OHRP Informed Consent FAQs;
- DAIDS Clinical Trial Protocol Documents Manual section 18.3.5

### 7.7. Electronic Informed Consent Guidance

Electronic informed consent (eIC) refers to the use of electronic systems and processes to convey
study-related information and to obtain and document informed consent. Electronic systems and
processes used must be in compliance with the FDA regulations at 21 CFR 11 and the DAIDS Policy
on the Use of Electronic Information Systems in Clinical Research. eICs may include the use of,
but not limited to, text, graphics, audios, podcasts, and interactive CRSs.

#### 7.7.1. eIC Process

- The eIC must contain the required elements of informed consent, unless the IRB/EC has
  approved a process that alters or waives some or all of the elements. (add hyperlink to section
  7.5)
- The information must be presented in a format that is understandable to the participants and
  all abbreviations should be spelled out the first time they are used.
- Take steps to accommodate persons who have impairments such as poor vision or have
difficulty with motor skills or are unfamiliar with electronic devices.
- The eIC process must allow participants the opportunity to ask questions and receive answers
  by any means or combination of methods, such as messaging, telephone calls, or
  videoconferencing before signing the eIC.
- If the eIC is interactive, it must be easy to use and allow the potential participant to go back
  and review information.

#### 7.7.2. Documenting eIC

- If the consent is obtained at the research CRS, the participant's identity will be verified, the
  contents of the eIC will be reviewed with the participant, study related questions from
  participant and witness will be answered, and the witness will also signed the eIC.
• If the consent process is conducted remotely, all interactive responses and signatures by participants, legally authorized representatives or other parties should be documented electronically by the software system.

• The system must capture the date that consent was given, and a copy of the consent must be provided to the person signing the form.

• The signed and dated hard copy of the eIC is given to the participant as per ICH E6 section 4.8.

7.7.3. eIC Confidentiality

The copy of the consent may be a printed copy of the eIC or an electronic copy that is transmitted to the participant. If the eIC is transmitted using a personal electronic device such as an iPhone, the participant should be advised of the risk of loss of confidentiality.

7.7.4. eIC Assent

The eIC process may also be used to obtain assent from children. The language and presentation of the information must be understandable to the child and the documentation of assent would be the same as that used for adult participants.

7.7.5. eIC IRB/EC Approval

The IRB/EC must review and approve eICs and any amendments to the eIC.

8. INFORMED CONSENT CONSIDERATIONS UNDER THE REVISED COMMON RULE

8.1. New Requirements upon implementation of the revised Final Rule/Common Rule (45 CFR 46)

**NOTE:** anticipated effective date of January 21, 2019

**SEE:** HHS - Revised Common Rule

8.1.1. Expanded Definition of “Legally Authorized Representative” (LAR)

The term legally authorized representative (LAR) has been expanded in the revised Common Rule and includes the following additional text: “If there is no applicable law addressing this issue, LAR means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject’s participation in the procedure(s) involved in the research”.

8.1.2. Concise Summary with “Key Information”

Under the Final Rule, consent forms will now require a concise summary of study activities, risks, and benefits to be presented to research participants in advance of the main body of the consent document. “Key information” must be included to facilitate a potential participant’s decision to participate or not. “Key Information” includes the following:

- The project is research with voluntary participation
- Summary of the research, including the purpose, duration, and procedures
- Reasonably foreseeable risks or discomforts
- Reasonable expected benefit
- Any alternative procedures or course of treatment

8.1.3. New Required Elements of Consent

These elements are contained in the Final Rule but are not yet implemented. In the interim, investigators may still consider informing participants in IC documents of the following, when appropriate.

New Basic Element to be included in IC documents: One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens needs to be included:

- A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
A statement that the subject’s information or biospecimens collect as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Three new Additional Elements to be included in IC documents, if applicable:

- “A statement that the subject’s biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit”;
- “A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions”; and
- “For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen)”.

8.1.4. Broad Consent and Secondary Research

The revised Common rules proposes the use of broad consent for the storage and use of biospecimens in future research with the proactive request of describing the general types of possible future research that may be done under a primary research study. This optional use of broad consent would allow the implementation of secondary research using identifiable private information and/or identifiable biospecimens without requiring a new study-specific IC form. Investigators will be allowed to continue to use biospecimens in secondary research with, at most, a limited IRB/EC/RE review or involvement, if any, and as long as there are no plans to share individual research results (IRRs) or incidental findings (IFs) with the individuals who provided these biospecimens as participants in the primary research.

Besides the specific broad consent elements described in the previous section, all basic elements of informed consent must be met as per §46.116(a), including informing participants that they are allowed to leave the research at any point, including secondary research studies, without penalty or loss of benefits. Furthermore, participants will also need to be reminded that the use of de-identified biospecimens in secondary research will be possible and that withdrawal of this permission may not be possible once the research has commenced. However, the Final Rule does prohibit IRBs/ECs/REs from waiving informed consent if participants were asked and declined to provide broad consent to the storage and use of their biospecimens and identifiable private information for secondary research.

Moreover, for studies where biospecimens are being stored at a central location or by third parties or collaborators, primary investigators working in association with these biobanks and each one of the new investigators conducting secondary studies will need to have clear plans for tracking the different levels of consent granted by participants. More importantly, primary investigators will need to ensure to honor the wishes of participants who declined consent for secondary research use, by disposing these biospecimens in a compliant and timely manner at the end of the primary research study.
8.1.5. Incidental Findings and Individual Research Results Disclosure from Secondary Research with Stored Biospecimens

In the Final Rule, secondary research use of identifiable biospecimens and identifiable private information is exempt from the Common Rule, if “the investigator does not include returning individual research results to subjects as part of the study plan.” The Final Rule does not address if this exemption applies to not returning results or incidental findings to at least one participant or to systematically to all participants. If the exemption is not available, the proposed research would be subject to regular IRB/EC/RE review. It is understood that the return of general or aggregate research findings would not prevent the use of this exemption.

HHS believes that returning individual research results may be beneficial not only to the participants, but to research in general by enhancing public trust and individuals’ willingness to participate. It is then recommended that when developing a study plan, sponsors and investigators carefully balance the utility of returning individual research results/incidental findings against the increased regulatory requirements resulting from not meeting the exemption criteria.

As clearly stated by the Secretary’s Advisory Committee on Human Research Protections (SACHRP) in Attachment C - Recommendations for Broad Consent Guidance: “The return of individual research results could be made to a single subject, a subset of the subjects, or to all of the subjects. This exemption does not require that the return of individual research results actually occur, but rather that the intention to return individual research results be part of the study plan—that is, that the return of results is a planned, premeditated activity contemplated in the protocol”

For example, if a study plan can forecast anticipatable incidental and significant findings from the primary and secondary research with identifiable biospecimens, that study plan should consider including these possible findings and their disclosure to the affected participants, which will make this research ineligible for an exemption from the Common Rule. However, even under this interpretation, a study plan would continue to meet the exemption criterion if it allows for reporting or disclosure to participants of incidental findings/individual research results that are clinically meaningful risks unrelated to the study’s design or endpoints (particularly and almost exclusive to primary research).
9. OTHER

9.1. DAIDS Informed Consent Templates

DAIDS created informed consent templates as tools to assist protocol teams, DAIDS networks, clinical research site (CRS) staff and other relevant stakeholders when developing protocol/sample and site-specific ICF documents for DAIDS supported and/or sponsored clinical research. Although DAIDS does not require the use of a standard IC form format, protocol and site-specific informed consent forms need to address each of the issues included in these templates, when relevant. However, the template language is not mandated to be used verbatim. Investigators are responsible for ensuring that all IC forms and related documents adhere to all applicable in-country, local, and institutional laws, regulations, guidelines, and policies. These templates can be found on the RSC’s website.

- DAIDS Sample Informed Consent Template for Stored Samples for Future Use and Instructions Page
- DAIDS Protocol Specific Informed Consent Template—General Use and Instructions Page

NOTE: the approach is “mandated concepts” rather than “mandated language”.

9.2. DAIDS Therapeutics Research Program (TRP) Guidance for the Development of Protocol Procedures to Address Reproductive Risk

DAIDS TRP created guidance for investigators and protocol teams to consider when developing clinical trials that will potentially include females and males of reproductive potential, in which there may be reproductive risks from the study product(s), strategies, or procedures. This document provides guidance on protocol inclusion/exclusion criteria, pregnancy testing and contraception requirements, follow-up for unintended pregnancy, pregnancy registries, and informed consent.

SEE: DAIDS Therapeutic Research Program Guidance for the Development of Protocol Procedures to Address Reproductive Risk

9.3. Informed Consent Process SOP Examples

DAIDS Informed Consent Process SOP examples are posted on the RSC’s website: Informed Consent Process Information. These documents are guidance resources; for use as reference only.
10.REFERENCES

This section will be added to the Final Version for general release.