

8	HUMAN SUBJECTS CONSIDERATIONS	8-1
8.1	Applicable US Federal Regulations and Guidelines	8-1
8.2	Training Requirements: Good Clinical Practice and Human Subjects Protection	8-2
8.3	IRB/EC Review and Approval	8-3
8.4	Other Regulatory Entities.....	8-5
8.5	Informed Consent and Assent	8-5
	8.5.1 Deliver all Required Information in a Manner that is Understandable to the Consenter	8-7
	8.5.2 Assure that Informed Consent is Obtained in a Setting Free of Coercion and Undue Influence	8-7
	8.5.3 Confirm that the Consenter Comprehends the Information	8-8
	8.5.4 Document the Process	8-8
	8.5.5 Reconsenting	8-9
	8.5.6 Storage of Informed Consent Forms	8-9
8.6	Special Populations	8-10
	8.6.1 Additional Considerations for Illiterate Consenters.....	8-10
	8.6.2 Additional Considerations for Research Involving Pregnant Women, Fetuses, and Underage Participants.....	8-12
	8.6.3 Additional Considerations for Prisoners	8-13
8.7	Confidentiality	8-13
8.8	Participant Costs for Study Participation.....	8-13
8.9	Participant Reimbursement for Study Participation	8-14
8.10	Access to HIV-Related Care.....	8-14
	8.10.1 HIV Counseling and Testing.....	8-14
	8.10.2 Care for Participants Living with HIV	8-14
8.11	Local Reporting Requirements	8-14

8 HUMAN SUBJECTS CONSIDERATIONS

8.1 Applicable US Federal Regulations and Guidelines

IMPAACT studies are funded by the United States (US) National Institutes of Health (NIH) and therefore they must be conducted in accordance with applicable sections of the US Code of Federal Regulations (CFR) as described below.

[CFR Title 45, Part 46 \(45 CFR 46\)](#): All IMPAACT studies must be conducted in accordance with 45 CFR 46 entitled “Protection of Human Subjects,” which includes subparts related to:

- Review of research by Institutional Review Boards/Ethics Committees (IRBs/ECs)
- Requirements for obtaining and documenting informed consent
- Additional protections and requirements when the following types of human subjects are involved in research:
 - 45 CFR 46 Subpart B: Pregnant women
 - 45 CFR 46 Subpart B: Fetuses
 - 45 CFR 46 Subpart B: Neonates
 - 45 CFR 46 Subpart D: Children
 - 45 CFR 46 Subpart C: Prisoners

Health Insurance Portability and Accountability Act (HIPAA): US sites participating in IMPAACT studies must also comply with [CFR Title 45, Parts 160](#) and [164](#), which cover “Standards for Privacy of Individually Identifiable Health Information” (also known as the “Privacy Rule”), which include subparts related to:

- Standards for use and disclosure of protected health information (PHI)
- Authorizations to use and disclose PHI or waivers of authorization
- Tracking of PHI uses and disclosures

Investigational New Drug (IND): IMPAACT studies conducted under an IND application are subject to additional regulation by the US Food and Drug Administration (FDA) and must be conducted in accordance with:

- [21 CFR 11](#) Electronic Records, Electronic Signatures
- [21 CFR 50](#) Protection of Human Subjects
- [21 CFR 54](#) Financial Disclosure by Clinical Investigators
- [21 CFR 56](#) Institutional Review Boards
- [21 CFR 312](#) Investigational New Drug Application
- [21 CFR 314](#) Applications for FDA Approval to Market a New Drug

Form FDA 1572: The Investigator of Record (IoR) is the individual at each site for an IMPAACT study who is responsible for ensuring that a clinical trial is conducted in accordance with the protocol, applicable US 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 Division of AIDS [DAIDS] Investigator of Record Form for non-IND studies).

The IoR is required to sign either a Form FDA 1572 (for IND studies) or a DAIDS Investigator of Record Form (for non-IND studies) to formally document agreement to conduct the study in accordance with the study protocol and applicable US regulations. The forms are completed and submitted to the DAIDS Protocol Registration Office (PRO) as part of the protocol registration process described in Section 11. The forms are available at <https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration-forms>, and guidance for completing them is provided in the DAIDS Protocol Registration Manual, which is available at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual>. In addition to signing either the Form FDA 1572 or the DAIDS Investigator of Record Form, the IoR must sign a study-specific Protocol Signature Page to formally document agreement to conduct the study in accordance with the protocol and all applicable protocol-related documents and in compliance with US regulations; standards of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP); IRB/EC determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements and institutional policies.

8.2 Training Requirements: Good Clinical Practice and Human Subjects Protection

DAIDS requires that all IMPAACT studies be conducted in accordance with *ICH E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (hereafter referred to as “GCP”): <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219488.htm>.

IMPAACT sites must comply with the DAIDS requirements for Human Subjects Protections (HSP) and Good Clinical Practice (GCP) Training, as per the Site Clinical Operations and Research Essentials

(SCORE) Manual, which is available at <https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations>.

For all site key personnel, required HSP and GCP training must have been completed within three years prior to participating in IMPAACT research and must be repeated every three years. For new site key personnel, documentation of required training must be completed within 90 days of assignment to an IMPAACT study and prior to functioning without direct supervision, unless training was received within the past three years and documentation is available.

The DAIDS glossary defines key personnel as individuals who are involved in the design and conduct of human subjects clinical research funded by the NIH. This includes any site personnel who have more than minimal involvement with the conduct of the research (such as performing study evaluations or procedures or providing the study intervention) or more than minimal contact with study participants or confidential study data, records, or specimens that are related to study conduct.

All other personnel who have minimal involvement in the conduct of the research or minimal study-related contact with participants should receive training that emphasizes the protection of participant privacy and confidentiality. Minimally involved personnel include drivers, couriers, clerical staff, and administrative staff.

Several acceptable training resources and methods are described in the DAIDS policy, including National Institute of Allergy and Infectious Diseases (NIAID) Learning Center training modules, which can be accessed at <https://learningcenter.niaid.nih.gov>. Other options and guidance related to training are included in Section 16.

As a condition for site-specific study activation, IoRs must document that all study site staff are appropriately qualified and trained to carry out their delegated duties. IoRs also must maintain adequate documentation of staff having completed required training. Documentation of HSP and GCP training must be maintained on-site and made available upon request to DAIDS personnel, study monitors, sponsor or regulatory authority representatives, site IRBs/ECs, and other US, local, and international regulatory entities.

8.3 IRB/EC Review and Approval

All IMPAACT studies must be reviewed and approved by IRBs/ECs responsible for oversight of research involving human subjects conducted at a site. A responsible IRB/EC registered with the US [Office for Human Research Protections](#) (OHRP) under a Federal Wide Assurance (FWA) must oversee IMPAACT research conducted at each site. In many cases, more than one IRB/EC is involved, for example, if a site is funded through a US institution with one or more sites in other countries. In such cases, all responsible IRBs/ECs must review and approve all required study-related documentation (as described further below). All studies must be reviewed and approved by all responsible IRBs/ECs prior to the initiation of study implementation. Thereafter, all studies must undergo continuing review at least annually.

45 CFR 46 requires sites located in the US to rely upon approval by a single IRB (sIRB) for cooperative research. To fulfill this requirement, the IMPAACT Leadership and Operations Center (LOC) selects an sIRB to provide oversight of IMPAACT studies conducted at US sites. The LOC coordinates submissions to and other communications with the sIRB. The sIRB reviews IMPAACT protocols and provides approvals applicable to participating US sites. The sIRB reviews and approves each participating site's informed consent and assent forms; additional review may occur if required by the local IRB per its agreement with the sIRB. As needed, the LOC and sIRB will arrange for training on sIRB policies and

procedures to be provided to IMPAACT site staff and will similarly ensure that relevant sIRB materials are made available to site staff.

All IRBs/ECs responsible for oversight of a given study must be listed on the Form FDA 1572 or the DAIDS Investigator of Record Form signed by the IoR.

The IRBs/ECs responsible for oversight of IMPAACT studies must meet the requirements of 45 CFR 46 and 21 CFR 56 (as applicable) and must be associated with an institution/organization that has received an FWA from OHRP, which formalizes the institution’s commitment to protect human subjects.

Additional information related to assurances is available on the OHRP website (<https://www.hhs.gov/ohrp/>). US regulations and the ICH Guideline for GCP specify the documents that sites are required to submit to their IRBs/ECs when obtaining initial and continuing review. Some IRBs/ECs may require additional documentation in support of their reviews; sites must comply with all IRB/EC requirements.

Documentation of all submissions to and all approvals from all responsible IRBs/ECs — and any other IRB/EC correspondence — must be maintained in on-site essential document files for each study. In addition, DAIDS requires submission of IRB/EC approval documentation and other documents to the PRO using the DAIDS Protocol Registration System (DPRS). Further information on the protocol registration process is provided in Section 11 and in the DAIDS Protocol Registration Manual. DAIDS requires all IRB/EC approval documentation to be labeled with the full protocol title, including the network protocol number, the DAIDS study ID number, the protocol version number, and the protocol version date. Although not required, sites are encouraged to request that IRBs/ECs note the effective and expiration dates of all approvals.

Table 8-1. Required IRB/EC Submissions for Initial Review and Approval (Prior to Study Initiation)

Documents Sites Must Submit to IRB/EC	Written Approval Required*
Protocol Version 1.0 (or first implementation version of the protocol, if not Version 1.0)	Yes
Site-specific Informed Consent Forms (ICF) and Assent Forms <i>Note: IMPAACT study ICFs typically contain information on participant reimbursement amounts and schedules; however, these may be approved through submission of separate materials.</i>	Yes
Investigator’s Brochure(s)** or Package Inserts**	No
Other Safety-related Information (if applicable)	No
Investigator of Record Current Curriculum Vitae	Yes
Participant Recruitment Materials Developed Prior to Study Initiation	Yes
Other Written Information for Study Participants Developed Prior to Study Initiation	Yes
Other Documentation Required/Requested by the IRB/EC	If required by IRB/EC
<p>*Based on U.S. regulations and the ICH Guideline for GCP, written approval is required for these documents. Additional approvals may be required by IRB/EC policies and procedures. If so, the required approvals must be obtained and filed.</p> <p>**Required for studies with investigational products.</p> <p>Note: All documents must be submitted to all IRBs/ECs responsible for oversight of study implementation at the site. Documentation of all submissions and approvals from all responsible IRBs/ECs must be maintained in on-site essential document files.</p>	

[45 CFR 46.109](#) requires that research be subject to continuing IRB/EC review at intervals appropriate to the degree of risk, but not less than once per year.

IoRs are responsible for ensuring timely submission of continuing review requests to IRBs/ECs so that no lapse in approval occurs for ongoing studies. The CTU PI is responsible for ensuring that the IoR fulfills this responsibility. As specified in the DAIDS Protocol Registration Manual, if a lapse occurs, the research at the site must stop, unless the IRB/EC finds that it is in the best interest of individual participants to continue participating in the research interventions or interaction. Enrollment of new participants cannot occur after the expiration of IRB/EC approval(s). Sites should contact their appropriate institute representative and/or institute program officer when there is any lapse and for additional guidance and information. Sites should submit IRB/EC lapse documentation (i.e., the site's documentation of the lapse to the IRB/EC and the IRB's/EC's response) to DAIDS PRO.

Continuing reviews must be conducted consistent with all applicable US and local regulations and IRB/EC policies and procedures. IoRs must submit documentation for review consistent with these regulations, policies, and procedures. IoRs must also submit documentation of continuing review to DAIDS PRO through the DPRS.

8.4 Other Regulatory Entities

In addition to oversight by IRBs/ECs, research conducted at many IMPAACT sites is subject to oversight by other regulatory entities. The DAIDS Protocol Registration Manual defines this type of entity as “Any group other than the local IRB/EC responsible for reviewing and/or approving a clinical research protocol and site-specific informed consent forms (ICFs) prior to implementation at a site. For example, in some states within the US, institutional approvals are required since these states have research regulations in addition to the federal human subjects protection regulations detailed in US federal regulations (45 CFR 46). In addition, at many non-US sites, other approvals may be required in addition to the local 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.”

All regulatory entities responsible for oversight of a given study must be listed on the Form FDA 1572 or the DAIDS Investigator of Record Form signed by the IoR.

IoRs are responsible for preparing submissions to and obtaining required initial and continuing review approvals from regulatory entities and for submitting documentation of the required approvals to DAIDS PRO using the DPRS. DAIDS also requires that copies of clinical trial applications submitted to in-country national regulatory authorities be provided to the DAIDS PRO using the DPRS.

8.5 Informed Consent and Assent

Informed consent is a process by which an individual voluntarily expresses their willingness to participate in research, after having been informed of all aspects of the research that are relevant to the decision. In the remainder of this section, persons who provide informed consent are referred to as “consenters.” These individuals may be study participants or the parents, legal guardians, or legally authorized representatives of study participants.

Written informed consent must be obtained before any study-specific procedures are performed with a potential study participant. For many IMPAACT studies, written assent must also be obtained from potential participants who are not of legal age or are otherwise not able to provide independent informed consent. All site staff involved in obtaining informed consent and assent must be designated on the study-specific delegation of duties log and listed on the Form FDA 1572 or DAIDS Investigator of Record

Form for the study. These staff must be qualified by education, experience, training, and knowledge of the study, as determined by the IoR, and appropriate training documentation must be available to support the IoR's delegation of responsibility for obtaining informed consent to these staff. See Section 11 for additional guidance related to the delegation of duties log.

For some IMPAACT studies, informed consent for both screening and enrollment is obtained in one step. For other studies, informed consent is first obtained for screening, and then informed consent for enrollment is obtained (in a second step) from participants found to be eligible during the screening process. Informed consent may also be requested for additional or optional procedures or for storage and possible future research use of biological specimens. Consenters may decline consent for optional procedures and still participate in a given study. ICFs may have separate sections to describe these procedures and separate signature blocks to document consent decisions for these procedures. Alternatively, a separate ICF may be used. Whenever a study involves human genetic testing, consenters must be provided with options to either consent to or decline this testing.

Because informed consent is considered an ongoing process, key elements of informed consent should be reviewed at all study follow-up visits.

For studies conducted at US sites, additional authorization to use or disclose PHI may be required if the site is regarded as a "covered entity" under HIPAA, and therefore subject to the Privacy Rule. This additional authorization may be included as part of the study ICF or may be a separate document. Authorization to use or disclose PHI must be approved by a responsible Privacy Board for the covered entity. The Department of Health and Human Services (DHHS) Office for Civil Rights has developed tools to help entities determine whether they are covered entities and subject to HIPAA.

The DAIDS guidance on [Review of Informed Consent Forms: Impact of the HIPAA Privacy Rule](#) clarifies how DAIDS informed consent reviews and protocol registration will be managed in the context of HIPAA. DAIDS will review ICFs for compliance with the Common Rule and US FDA regulations and DAIDS requirements, but not for Privacy Rule compliance.

Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the informed consent process is described below. Additional informed consent process information promulgated by DAIDS is available at <https://rsc.niaid.nih.gov/clinical-research-sites/informed-consent-process-information>. Refer to Section 4.8 of the ICH Guideline for GCP and the DAIDS SCORE Manual.

All IMPAACT sites must establish and maintain standard operating procedures (SOPs) for obtaining informed consent and assent that address all aspects of the informed consent and assent processes consistent with all applicable regulations and guidelines, DAIDS policies and procedures, and site IRB/EC policies and procedures; sites should also note that SOPs may need to be modified and/or augmented to meet individual IMPAACT study protocol specifications (e.g., in study-specific addenda). Additional key considerations for SOPs established for IMPAACT studies include methods for:

- Ascertaining whether a potential participant is of legal age or is otherwise able to provide independent informed consent
- Ascertaining legal guardianship
- Ascertaining whether a consenter is literate and who may serve as a witness to informed consent processes conducted with illiterate consenters
- Ascertaining comprehension before proceeding to an informed consent decision

- Determining whether assent will be obtained in the presence of a parent or guardian
- Addressing the extent to which potentially sensitive information collected in studies of children and adolescents (e.g., drug and alcohol use, sexual activity) will be reported to parents or legal guardians
- Obtaining assent from participants who were enrolled prior to the age of assent
- Obtaining informed consent from participants who were enrolled prior to the age of independent informed consent

Sites are encouraged to incorporate Community Advisory Board (CAB) input into these SOPs and to seek IRB/EC review and approval of these SOPs.

US regulations (45 CFR 46 and 21 CFR 56) specify the elements of informed consent that must be conveyed to consenters through the informed consent process. It is the responsibility of the IoR, and by delegation all study staff involved in conducting the informed consent process, to deliver all required information to consenters. Based on the reviews completed as part of the IMPAACT protocol development and study activation processes, there is assurance that once a site is activated for an IMPAACT study, a site's ICFs include all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate ICF. It also is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to the consentor
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the consentor comprehends the information
- Document the process

Further guidance related to each of these requirements and processes is provided in the subsections below.

8.5.1 Deliver all Required Information in a Manner that is Understandable to the Consentor

The informed consent process should be conducted in the consentor's preferred language and should reflect whether the consentor is determined to be literate per site SOPs.

If the consentor is literate, begin the informed consent process by providing the consentor with a copy of the ICF to read. Also provide the consentor with any other informational materials developed to complement the ICF. If the consentor is not literate, read the materials to the person. After the consentor has read (or has been read) the materials, verbally review the information provided. A checklist or the ICF itself may serve as a useful guide for this. For example, note the main points described in each paragraph of the ICF and ask if the consentor has questions or concerns about each point. Listen carefully to the questions and/or concerns expressed by the consentor and discuss these thoroughly. Take as much time as needed to address each question or concern.

If the consentor is not literate, an impartial literate witness must be present during the entire informed consent process. See Section 8.6.1 below for more information regarding illiterate participants.

8.5.2 Assure that Informed Consent is Obtained in a Setting Free of Coercion and Undue Influence

During informed consent discussions, take care to not overstate the possible benefits of the study, nor to understate the risks. Also describe the alternatives to study participation and emphasize that the availability of medical care and other services (outside the study) will not be affected by the consentor's

decision whether to take part in the study. Encourage the consentor to take as much time as needed — and to talk about study participation with others if the consentor chooses — before making a decision.

When a witness is present during the informed consent process, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the consentor, with emphasis on the fact that the witness is there as a protection for the consentor, not as an agent of the study per se.

8.5.3 Confirm that the Consentor Comprehends the Information

The consentor must not be asked to agree to take part in the study, or to sign or make their mark on the ICF, until they fully understand the study. Study staff are responsible for ensuring that each consentor understands all aspects of study participation before signing or marking the ICF.

A variety of approaches can be taken to assess comprehension. Unless a specific method is designated as required to be used in a given study, methods used should be as specified in site SOPs. These methods may include a semi-structured checklist to guide a discussion in which the consentor responds to open-ended questions designed to elicit understanding of key concepts; other types of documented discussions with the consentor; and structured knowledge quizzes administered to the consentor.

Regardless of the method used to assess comprehension, if the assessment indicates misunderstanding of aspects of the study, study staff should review those aspects again until the consentor fully understands them. If after additional review and discussion the consentor is not able to demonstrate adequate understanding, the consentor should not be asked to sign or mark the ICF. Similarly, if the consentor has concerns about possible adverse impacts if they were to provide consent or indicates that they may have difficulty adhering to the study requirements, the consentor should not be asked to sign or mark the ICF unless or until such issues can be resolved to the satisfaction of the consentor and the IoR or designee.

8.5.4 Document the Process

US regulations require that informed consent be documented through the use of a written ICF approved by the responsible IRBs/ECs and signed and dated by the participant or the participant's legally authorized representative at the time of consent. In general, the same documentation conventions that apply to informed consent processes are expected to apply for assent processes.

All signature and date blocks on the ICF should be completed in ink. Legal names should be used. Fabricated or falsified names should never be used. Initials may not be used in place of a consentor's full surname, and it is strongly recommended that initials not be used in place of a consentor's full first name. However, if a consentor commonly signs their name using an initial for their first name, the initial may be used, provided this practice is acceptable per the policies of the site institution(s). Character symbols (e.g., Chinese characters) are acceptable in countries that use them.

If the consentor is not literate, the witness who was present during the informed consent process must sign and date the ICF to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the consentor, and that informed consent was freely given by the consentor.

The DAIDS SCORE Manual lists detailed requirements and suggestions for documenting the informed consent process. Sites must comply with all requirements and are encouraged to comply with all suggestions. To assist with compliance, study staff may use informed consent coversheets (or other similar tools). Sites choosing to use coversheets should identify the coversheets as source documents in

their SOPs for source documentation and should use the coversheets consistently to document each informed consent process conducted with each consentor. All informed consent documentation must be maintained on file in participant study records.

In addition to completing the documentation requirements of the ICF itself, each informed consent process should be documented in a signed and dated chart note. The note should document that informed consent was obtained before conducting any study procedures. The note also should document adherence to the informed consent requirements outlined in the DAIDS SCORE Manual. However, if an informed consent coversheet (or other similar tool) is used, it is not necessary to transcribe information recorded on the coversheet (or other tool) into the chart note.

Data required to document informed consent and assent decisions will also be entered into study-specific eCRFs.

Regulations require that consentors be given a copy of their signed ICF. If a consentor opts not to receive a copy, this should be documented, and the consentor should be offered an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full ICF. The same approach should generally be taken, when applicable, with assent forms.

8.5.5 Reconsenting

As indicated above, IMPAACT site SOPs for obtaining informed consent should describe methods of obtaining assent from participants who were enrolled prior to the age of assent and for obtaining informed consent from participants who were enrolled prior to the age of independent informed consent. IoRs and designated study staff are responsible for determining when previously-enrolled study participants reach the age of assent and/or the age of independent informed consent and for conducting and documenting required assent and informed consent processes with these participants. As assent and consent requirements change over time with participant age, the most up-to-date assent and consent decisions are taken to apply. For example, if a participant previously-enrolled at 16 years of age is not willing to provide written informed consent for continued study participation when she reaches 18 years of age, her decision should be taken to override the prior consent decision made when she was first enrolled in the study.

Over the course of a study, new information may become available that may affect prior informed consent and assent decisions. For example, protocol-specified procedures may be modified or new safety- or risk-related information may come to light. In such cases, the study protocol, sample ICFs, and sample assent forms are typically amended, and study staff are required to obtain re-consent (and re-assent if applicable) for the continued study participation of previously-enrolled participants. Further detailed written guidance on re-consenting and re-assenting requirements is typically provided to sites by the protocol team. In addition, the DAIDS Protocol Registration Manual specifies that re-consenting is expected to occur immediately (i.e., without delay no later than 5 business days) upon obtaining all required IRB/EC and regulatory entity approvals of revised ICFs (and assent forms), usually by or at the participant's next study visit.

8.5.6 Storage of Informed Consent Forms

IMPAACT sites must maintain, in a confidential and secure manner, the complete, original, signed and dated ICFs (and assent forms if applicable), of all persons who are screened for and/or enrolled in IMPAACT studies, in accordance with the specifications of the study protocol and the study-specific manual of procedures (see also Section 8.7).

8.6 Special Populations

8.6.1 Additional Considerations for Illiterate Consenters

US regulations and the ICH Guideline for GCP specify additional protections that must be in place when obtaining informed consent from illiterate consenters. A witness who is literate in the language in which the informed consent discussion is conducted must be present during the entire informed consent process undertaken with an illiterate concenter. The ICH guideline identifies an impartial witness as a person who is independent of the study and cannot be unfairly influenced by people involved with the study. This witness need not be totally unaffiliated with the study. It may be possible, for example, to designate a participant advocate who would be available at each site. The witness will sign and date the ICF to attest that the information in the consent form was accurately explained to, and apparently understood by, the concenter, and that informed consent was given freely by the concenter. Site SOPs for obtaining informed consent should specify procedures to be followed when obtaining informed consent from illiterate persons and should define who may serve as the witness to the informed consent process. Refer to Figure 8-1 for a summary of considerations for obtaining informed consent from illiterate consenters. Figure 8-2 provides an example of completion of informed consent signature blocks for illiterate consenters.




Additional considerations for documenting the informed consent process for illiterate consenters are as follows:

- The study staff member who conducts the informed consent process should document the concenter's illiteracy in the study chart.
- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs (with the endorsement filed in study-specific essential document files), the study staff member who conducts the informed consent process should enter the concenter's name below the concenter's printed name block on the ICF, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry. The concenter's signature date should be completed in the same manner.
- The concenter should make their mark (e.g., thumbprint) in the concenter's signature block.

Figure 8-1. Summary of Considerations for Obtaining Informed Consent from Illiterate Consenters

- Sites must specify procedures for obtaining and documenting informed consent from illiterate persons in their SOP for obtaining informed consent. These procedures must be consistent with the DAIDS SCORE Manual and must be followed each time informed consent is obtained from an illiterate consenter. It is recommended that sites seek IRB/EC review and approval of these procedures.
- An impartial witness must be present during the entire informed consent process with an illiterate consenter. The witness must sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter.
- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.
- Take care to minimize the perception of coercion due to the presence of the witness.
- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should print the consenter's name below the consenter's printed name line on the informed consent form, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see Figure 8-2 below).
- The consenter should make their mark on the consenter's signature line.
- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should enter the date upon which the consenter marked the ICF below the consenter's signature date line, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see Figure 8-2 below).
- For more information, see Section 4.8 of the ICH GCP guidance and the DAIDS SCORE Manual.

Figure 8-2. Example of Completed Informed Consent Signature Blocks for Illiterate Consenters

SIGNATURES		
Participant Name	Participant Signature	Date
Mary Phiri		25 NOV 2014
<i>Participant name and date written by Martha Moore. MM 25 NOV 2014</i>		
Martha Moore		25 NOV 2014
Name of Staff Person Conducting Consent Discussion	Study Staff Signature	Date
Debra Ross		25 NOV 2014
Witness Name	Witness Signature	Date

8.6.2 Additional Considerations for Research Involving Pregnant Women, Fetuses, and Underage Participants

IMPAACT studies frequently involve pregnant women, women who may become pregnant, fetuses, infants, and children.

[45 CFR 46.201](#) specifies additional considerations for research involving fetuses, pregnant women, and neonates and research involving children in Subparts B and D, respectively. These subparts outline additional requirements for IRBs/ECs when reviewing research involving these vulnerable populations and assessing the relative risks and benefits of the proposed research.

DAIDS requires documentation of the IRB/EC designation of the pediatric risk/benefit category from 45 CFR 46.404-407 and 21 CFR 50.51-54 and IRB/EC approval for involvement of children based on the determination specified by that category. This requirement applies to the initial and continuing reviews of study protocols and to any subsequent reviews of protocol amendments involving potential study risks or benefits. The documentation may be provided in IRB/EC approval letters or in other official correspondence from the IRB/EC and must be included in submissions to DAIDS PRO. Additional guidance can be found in the DAIDS Enrolling Children in Clinical Research Policy located at: <https://www.niaid.nih.gov/research/daids-clinical-research-protocol-informed-consent>.

Obtaining and documenting consent for participation of infants and children may involve obtaining consent from one or both parents, a legal guardian, or other legally authorized representative. DHHS regulations at [45 CFR 46.102\(I\)](#) define a legally authorized representative as 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. Thus, under 45 CFR 46.102(I), the determination of who may be a legally authorized representative is a matter of state or local law. It is highly recommended that site SOPs for obtaining informed consent and assent, including defining the

minimum age for independent consent and defining and ascertaining legal guardianship, be submitted for review and approval by responsible IRBs/ECs prior to initiation of IMPAACT studies involving infants and children.

8.6.3 Additional Considerations for Prisoners

IMPAACT does not plan to conduct any studies that recruit, screen, or enroll participants from a prison setting. However, it is possible that persons enrolled in IMPAACT studies could become incarcerated during follow-up. [45 CFR 46 Subpart C](#) specifies additional considerations for protection of prisoners as subjects in biomedical and behavioral research including enhanced IRB/EC review requirements and a requirement to obtain approval for prisoner participation from the Secretary of the US DHHS. IMPAACT sites will comply with these requirements prior to involving prisoners in any IMPAACT study.

8.7 Confidentiality

Study site staff will make every effort to maintain the confidentiality of study participants and information that can be linked to them; however, absolute confidentiality cannot be guaranteed. Unless otherwise specified in the study protocol, sites shall not submit any of the following participant identifying information to the Statistical and Data Management Center or other external entity: participant names (including partial and initials), addresses, phone or fax numbers, email addresses, medical record numbers, health insurance beneficiary numbers, or account numbers.

Authorized representatives of the following organizations are granted access to participant study records as needed to assess the quality of study conduct:

- NIH
- Collaborating pharmaceutical companies
- Clinical site monitors
- IMPAACT Operations Center, Statistical and Data Management Center, and Laboratory Center
- Site IRBs/ECs and regulatory entities
- US OHRP
- US FDA
- Other US, local, and international regulatory authorities

In addition to efforts undertaken by site staff to ensure confidentiality, a Certificate of Confidentiality (CoC) is deemed issued for IMPAACT under the terms of the NIH award. The certificate protects US sites from being compelled to disclose study-related information by any US federal, state, or local civil, criminal, administrative, legislative act or other proceedings. The provisions of the CoC, as well as its limitations (e.g., in cases of reportable harm to self or others), will be included in the ICF and will be explained to participants during the informed consent process for each study to which the certificate applies. See Section 7 for further details regarding the CoC.

8.8 Participant Costs for Study Participation

Unless otherwise specified in the study protocol, IMPAACT study procedures are performed at no cost to study participants.

8.9 Participant Reimbursement for Study Participation

Pending IRB/EC approval, participants may be reimbursed for their time and effort when taking part in IMPAACT studies, and/or be reimbursed for costs associated with travel to study visits, time away from work, childcare, etc. Guidance should be sought from local community representatives on appropriate site-specific reimbursement types, amounts, and schedules prior to final IRB/EC approval.

8.10 Access to HIV-Related Care

8.10.1 HIV Counseling and Testing

Most IMPAACT studies involve HIV testing. All such testing will be provided in the context of HIV pre-test, risk reduction, and post-test counseling. Participants (or their parents or guardians) must receive their HIV test results and associated counseling to enroll in IMPAACT studies, as specified by study eligibility criteria.

8.10.2 Care for Participants Living with HIV

Most IMPAACT studies will identify persons with HIV, either as part of the study screening process or during follow-up of enrolled participants. IMPAACT studies cannot provide long-term care and/or treatment to persons living with HIV; however, each protocol contains information on HIV-related care and support that may be available to study participants. Plans for post-study access to agents provided through an IMPAACT study from which participants are benefiting are discussed early in protocol development and addressed in each protocol.

All IMPAACT sites are required to be familiar with current local standards of care for HIV prevention and treatment and to maintain resource lists and SOPs for referral of persons newly diagnosed and living with HIV. Study participants should be actively referred to local standard of care providers for aspects of their care and treatment that cannot be provided through the study in which they are participating. This may include HIV-related care, reproductive health care, well baby, and under 5 care, and specialized care to further evaluate and treat adverse events identified during study participation. Similar approaches should be taken for referral of participants to social service providers, e.g., for housing and food insecurity.

8.11 Local Reporting Requirements

IMPAACT study staff will comply with all applicable local reporting requirements such as communicable diseases and/or child abuse and neglect identified among IMPAACT study participants to local authorities. Participants will be made aware of all reporting requirements during the study informed consent process.