



11 HUMAN SUBJECTS CONSIDERATIONS

11.1 Applicable US Federal Regulations and Guidelines

IDCRC protocols/studies are funded by the United States (US) Department of Health and Human Services (DHHS) 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 IDCRC 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 IDCRC 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): IDCRC studies conducted under an IND application are subject to additional regulation by the US Food and Drug Administration (FDA) and must be conducted (at the respective sites) 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 IDCRC 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.

The IoR is required to sign either a Form FDA 1572 (for IND studies) or equivalent form for non-IND studies (e.g., a Division of Microbiology and Infectious Diseases [DMID] Investigator of Record Form) 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 FHI360/the Clinical Operations Unit (COU) for review and upload to the DMID Site Essential Regulatory Document (SERD) Electronic System. Current versions of both forms, as well as form completion instructions, are available on the DMID CROMS site; <https://www.dmidcroms.com/CRS/ERDG/SitePages/EssentialRegulatory.aspx>.

In addition to signing either the Form FDA 1572 or the DMID Investigator of Record Form, the IoR must sign a study-specific Protocol Signature Page (PSP) 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 (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.

11.2 International Council for Harmonisation Guideline for Good Clinical Practice

DMID requires that all IDCRC studies be conducted in accordance with the ICH Guideline for GCP, which is available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>.

11.3 Human Subjects Protection Training

NIH requires that all personnel involved in the design or conduct of human subjects research must receive training in the protection of human subjects. From <https://www.niaid.nih.gov/research/human-subjects-research-training-sop>

Key personnel indicate individuals that are involved in the design and/or conduct of human-subjects clinical research. More specifically, this includes any site personnel who have more than minimal involvement with the conduct of the research (such as performing study evaluations/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.

IDCRC sites must comply with the DMID guidance on *Human Subjects Protections (HSP) and GCP Training Requirements*, which is available at <https://www.dmidcroms.com/CRS/Resources/Training/SitePages/TrainingHome.aspx>.

For all site key personnel, required training must have been completed within three years prior to participating in IDCRC research and must be repeated every three years. For site key personnel, who join the study team after activation, documentation of required training must be completed within 90 days of assignment to an IDCRC study and prior to functioning without direct supervision.

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 includes drivers, couriers, clerical staff, and administrative staff.

Several acceptable training resources and methods are described in the DMID policy, including NIAID Learning Center training modules which can be accessed at <https://learningcenter.niaid.nih.gov>.

11.4 IRB/EC Review and Approval

All IDCRC studies must be reviewed and approved by IRBs/ECs responsible for oversight of research involving human subjects conducted at a site (45 CFR 46 and 21 CFR 56 – as applicable). A responsible IRB/EC registered with the US [Office for Human Research Protections](#) (OHRP) under a Federal Wide Assurance (FWA) must oversee IDCRC research conducted at each site. Each study must be reviewed and approved by the responsible IRBs/ECs prior to the initiation of study implementation. Thereafter, each study must undergo continuing review at least annually, unless specifically not required by the IRB of record, as may occur in minimal risk studies.

By law, all US sites (with a few exceptions – Training Awards, domestic sites where more than one single IRB review is required by law, including tribal law governing an American Indian or Alaskan Native tribe) a participating in an IDCRC study that is conducted at more than one US site must use the single IRB (sIRB) contracted by the IDCRC LG. Non-US based sites are not subject to the policy requiring the use of the sIRB.

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

Additional information related to assurances is available on the OHRP website (<https://www.hhs.gov/ohrp/>). US regulations and the ICH Guidelines 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 an on-site Investigator Site File for each study. In addition, DMID requires submission of IRB/EC approval documentation and other documents to the DMID SERD Electronic System. All IRB/EC approval documentation should be labeled with the full protocol title, including the protocol 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.

CONTINUING REVIEW

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. Minimal risk studies may be exempted from continuing reviews at the discretion of the IRB/EC.



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 VTEU Site PI is responsible for ensuring that the IoR fulfills this responsibility. 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/EC's response) to the IDCRC COU and DMID.

sIRB continuing review for protocols where FHI 360 has submitted the original submission will be handled by FHI 360.

11.5 Other Regulatory Entities

In addition to oversight by IRBs/ECs, research conducted at many IDCRC sites is subject to oversight by other regulatory entities; other entities may include “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 DMID 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 DMID through FHI 360.

11.6 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.

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
- IDCRC COU, Statistical and Data Coordinating Center/Statistical and Data Sciences Unit



- (Emmes/SCHARP, respectively), and Laboratory Operations Unit (LOU)
- Responsible single IRBs/IRBs
 - US FDA
 - Local drug regulatory authorities
 - Other US, local or international regulatory authorities

11.7 Participant Costs for Study Participation

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

11.8 Participant Reimbursement for Study Participation

Pending IRB/EC approval, participants may be reimbursed for their time and effort when taking part in IDCRC 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.

DMID guidelines

<https://www.dmidcroms.com/Shared%20Documents/Payment%20for%20Participation.pdf>

11.9 Communicable Disease Reporting Requirements

IDCRC study staff will comply with all applicable local requirements to report communicable diseases identified among IDCRC study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.