Guide for an NIH IRB serving as the IRB of record for multi-site studies

Version #: 1.0 **Next Review Date: June 2018**

Approved Date: June 2016 **Review Interval Period: Biennial**

PURPOSE

The purpose of this guide is to describe the processes and procedures to be followed by an NIH IRB when it serves as the IRB of record for non-NIH sites participating in a multi-site study, and for non-NIH sites participating in a multi-site protocol who are ceding IRB review of their research activity to an NIH IRB. The guide describes the flow of IRB-related information between the sites and the NIH IRB serving as the IRB of record, as well as information, timelines, and documentation required for the initial protocol review and subsequent IRB submissions. It also sets forth the process and requirements for other review decisions over the course of the protocol.

DEFINITIONS

Coordinating Center (Entity) for Multi-site Studies: A Coordinating Center is the entity that is responsible for overall planning, document collection, monitoring and communication among all sites participating in a multi-site research protocol. A Coordinating Center may also be responsible for data management and analysis and may be designated either by a sponsor or by mutual agreement of the participating sites. The sponsor may delegate some of its responsibilities to the Coordinating Center (For additional information related to Coordinating Centers and IRB oversight of such Centers, see NIH HRPP Standard Operating Procedure (SOP) 20C-Responsibilities When the NIH Intramural Research Program serves as a Coordinating Center for a Multi-site Trial or Serves as the IRB of Record for a Non-NIH Coordinating Center in the **Links** section).

Coordinating Center IRB Liaison (CC IRB Liaison): Individual/s who coordinate/s with the NIH PI, extramural participating sites, and the NIH IRB for the submission and dissemination of protocol-related documents, IRB determinations and communications.

Engaged in Human Subjects Research: An institution becomes "engaged" in human subjects research when its employees or agents (all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility) (i) intervene or interact with living individuals for research purposes; or (ii) obtain individually identifiable private information for research purposes [45 CFR 46.102(d),(f)]. Solicitation of consent by Participating Site staff would be considered engagement. The comprehensive definition of institutional engagement in research can be found in OHRP's 2008 Guidance on Engagement of Institutions: http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-engagement-of-institutions/index.htmlengagement

Federalwide Assurance: A formal written, binding commitment that is submitted to a federal agency in which an institution promises to comply with applicable regulations governing non-exempt human subjects research conducted or supported by HHS and stipulates the procedures through which compliance will be achieved. Since December 31, 2005, the Office for Human Research Protections (OHRP) only recognizes Federalwide Assurances.

Institutional Designee: An individual identified in the reliance agreement by the Participating Site to receive documents (in addition to the participating site PI) on behalf of the relying institution and who will work directly with the Coordinating Center IRB Liaison (if there is one), the site PI(s), and others at the Participating site to coordinate and complete site requirements that are necessary for protocol-related activities.

IRB of Record: The IRB responsible for centrally reviewing a research protocol for multiple sites engaged in multi-site cooperative research. This IRB is responsible for review and oversight of research and for determining whether the research meets the regulatory criteria for approval at a Participating Site that has ceded review to this IRB.

Multi-Site Protocol: Multi-site research/protocols refer to projects that will be conducted at more than one location. Usually a multi- site study involves conduct of a protocol carried out at more than one medical institution or site. Sites may also include schools, nursing homes, community rehabilitation facilities, private practices, individual homes, etc. As part of the protocol application, the investigator shall disclose the entity that will serve as the Coordinating Center for the protocol.

NIH IRB (IRB): The NIH IRB panel that will serve as the IRB of Record for all participating sites that sign a Reliance Agreement with the NIH.

NIH Principal Investigator (PI): The lead intramural investigator responsible for the conduct and integrity of the protocol at the NIH and for submitting the protocol to the NIH IRB. Note that the NIH PI may not be the overall PI for a multi-site protocol.

Participating Site: A site where non-exempt human subjects research is occurring (e.g. staff member are engaged in human subjects research or have access to private records of identifiable individuals that are being used for research). The Participating Site is the actual place where the research activity takes place. The Participating Site's location may be different from the location of the IRB review. In the absence of a policy or regulation requiring single review, a participating site may or may not be relying on the IRB of Record.

Reliance Agreement: The agreement used when the NIH is involved in a research collaboration with a Federalwide Assurance-holding institution. For the purposes of this guide, reliance agreements indicate situations when a non-NIH Participating Site defers IRB review responsibility to an NIH IRB in order to avoid dual review. The terms Authorization Agreement (AA) and Reliance Agreement are used interchangeably; however, Reliance Agreement is the preferred term at NIH and is used throughout this guide. This can be either a protocol-specific

agreement or a program-wide agreement. For specific information regarding Reliance Agreements, please see NIH HRPP SOPs 20 and 20A in **Links** below.

Site PI: A Site PI is the lead investigator at a Participating Site.

OVERVIEW

When the NIH IRB serves as the IRB of Record for a multi-site protocol, the NIH Pl will provide the IRB with the names and contact information of the individual or office at the Participating Site(s) that is responsible for protocol oversight. On a case by case basis, an NIH IRB may serve as the IRB of record for a multisite study when the lead PI is not an NIH investigator. Additionally, an appropriate level of information regarding the site and the local investigator will be provided so the IRB can evaluate the qualifications of the investigator and the adequacy of the site before approving research to be conducted at the site. Information about the site should be provided using the Local Context Worksheet and associated attachments. The IRB may request additional information about the site as necessary.

When the NIH IRB serves as the IRB of Record, it will work closely with the CC IRB Liaison or other appropriate individual(s) and/or Coordinating Center, if one is designated, to ensure adequate mechanisms are in place to facilitate communications between the IRB of Record and the Participating Sites relying on the NIH IRB.

When the NIH IRB reviews a multi-site protocol where the NIH Principal Investigator (Pl) is responsible for the Coordinating Center (that may or may not be engaged in human subjects research), the NIH IRB determines whether the oversight responsibilities of the Coordinating Center are appropriately identified to safeguard the rights and welfare of research participants, and is in accordance with OHRP Guidance on Engagement in Research. The NIH IRB will determine and document that the Coordinating Center has sufficient mechanisms in place to ensure (i) adherence to 45 CFR 46, and if applicable 21 CFR 50 & 56, and Good Clinical Practices at all sites; (ii) that the privacy of subjects and the confidentiality of data are adequately maintained; and (iii) that the protocol(s) is reviewed and approved by an IRB for the collaborating institution(s) engaged in human subjects research. Additionally, the NIH IRB will confirm that there is a reliance agreement between the non-NIH Coordinating Center and NIH.

PROCEDURES FOR PARTICIPATING SITES RELYING ON THE NIH IRB AS THE IRB OF RECORD

When the NIH IRB serves as the IRB of Record, the protocol and model consent will first be reviewed and approved by the NIH IRB as per NIH HRPP SOP 8 (see Links) prior to distribution to any of the Participating Sites.

Step 1: Process for Adding a Site to a Protocol

For Participating Sites who rely on a NIH IRB through a Reliance Agreement the NIH Pl must submit the following documentation for initial IRB review and approval:

- Confirmation of compliance with Human Subjects Protection training for the Participating Site lnvestigator and Associate Investigators at the site;
- Current CV, or biosketch, for the Participating Site lnvestigator listed on the Reliance Agreement that provides information supporting the qualifications for his/her role in the research study;
- Revised study application listing the Participating Site in the NIH electronic submission system (iRIS or PTMS);
- Amended protocol that lists the Participating Site and outlines the study-related responsibilities of the Site PI;
- Site-specific protocol appendix (if the site has one) that they are using for local instructions/information that will be appended to the primary protocol document;
- Site-specific consent document based on the IRB approved model consent form;
- Local context worksheet and applicable attachments.

The information provided by the Participating Site, including the local context worksheet and the site specific consent, may be reviewed by a convened IRB or by expedited review by the IRB Chair and/or designee.

The NIH IRB Chair or designee may choose to communicate with the Institutional Designee at the site to assess or clarify local context issues, or to obtain additional information. Information relevant to local context will be provided to the IRB for consideration when reviewing research to be performed at locations outside the NIH.

Once the Reliance Agreement is fully executed (signed by the Institutional Official/Designee at both sites) and the NIH IRB has approved the site, a notice of IRB approval will be sent to the PI and the Institutional Designee of the Participating Site by the IRB. If a programmatic reliance agreement is already in place with the site, then the notice will be sent once the NIH IRB approves the site.

Step 2: Reportable Events—Responsibilities and Procedures

Unanticipated problems involving risks to subjects or others, adverse events, protocol deviations and/or serious or continuing noncompliance are reported to the NIH IRB in accordance with requirements set forth in NIH HRPP SOP 16-Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations and SOP 16A-Allegations of Non-compliance with Requirements of the NIH Human Research Protection Program (HRPP) (See Links) and consistent with the terms of the Reliance Agreement.

- Participating Sites must assess and determine if an event fulfills the criteria for prompt reporting as per NIH SOP 16 and the approved protocol. It will then submit the required information to the NIH IRB via the NIH PI, using a paper version of the NIH problem form.

- The NIH PI or designee will submit all received reportable events that require prompt reporting to the NIH IRB and as required by NIH SOP 16 and 16A using the electronic NIH problem report form. The NIH PI will also attach the original problem report form completed by the site.
- If a reportable event does not require prompt reporting as per NIH SOP 16 and the approved protocol, the information will be provided as part of the Continuing Review.
- The NIH IRB will make a determination for events submitted on the problem report form and provide a response to the Participating Site PI, NIH study contacts, and the NIH PI.
- If an NIH IRB determination of an unanticipated problem or serious and/or continuing noncompliance is made requiring reporting to OHRP and, as applicable, the FDA, the NIH IRB will provide a copy to the Participating Site where the event occurred.
- If the NIH IRB determines that it must report serious or continuing non-compliance determinations, suspensions or terminations or the findings of an investigation to OHRP, the FDA and/or other oversight entities, it will notify the Participating Site in advance. When feasible, the NIH OHSRP will provide the Participating Site the opportunity to review and comment on the report before it is sent to OHRP, the FDA or others, provided that the Participating Site promptly provides any comments on the report before it is finalized and sent to OHRP and as applicable, the FDA.
- A copy of the final report that is sent to OHRP and, as applicable, the FDA, will also be sent to the Participating Site's Institutional Designee and PI by OHSRP.

Step 3: Continuing Review—Responsibilities and Procedures

The NIH PI and/or the CC IRB Liaison will notify each Participating Site regarding information required for continuing review, including updated information regarding local context.

- The Participating Site will complete the information on the Local Context Continuing Review form. Each Participating Site will submit the required information for continuing review to the NIH PI at least 2 months prior to the continuing review deadline.
- The NIH PI and/or Coordinating Center will review the Participating Site's submission for accuracy and completeness.
- The NIH PI will submit a single continuing review application to the NIH IRB that includes continuing review information from all Participating Sites that are subject to the reliance agreement.
- The NIH IRB will review all submitted materials.
- The NIH IRB will communicate the results of the review to the NIH PI, the Participating Site PIs, and the Institutional Designee(s) of all Participating Sites.

Step 4: Amendments—Responsibilities and Procedures

- The NIH PI and CC IRB Liaison will submit all study-wide amendments to the NIH IRB.
    - The NIH PI will submit study-wide protocol amendments, such as changes to the substantive content of the protocol, to the NIH IRB.

    - If the study-wide protocol amendment requires changes to the model documents (informed consent forms/recruitment materials), a tracked and clean version will be submitted for review.
    - If a new site is added, the NIH PI will also submit a Local Context worksheet for the proposed site and revised study application, following the procedure outlined above in step 1.
- The NIH PI and CC IRB Liaison will submit all site-specific changes being proposed by any Participating Site as an amendment to the NIH IRB.
    - The Participating Site will submit a request for an amendment with all supporting documentation to the NIH IRB via the CC IRB Liaison and NIH PI.
    - The Participating Site will provide, with the request for an amendment, tracked and clean versions of any modified documents.
    - The Participating Site will not initiate any changes until IRB approval notification is received.
- The NIH IRB will review protocol and site-specific amendments.
    - The NIH IRB will communicate the results of the review to the NIH PI, CC IRB Liaison, the local Site PIs(s), and the Institutional Designee(s).

Step 5: Translations—Responsibilities and Procedures

- The enrollment of non-English speaking subjects must be approved by the NIH IRB.
- Short Form Process:
    - The use of the short form process must be approved by the NIH IRB on a site-specific basis.
    - This may be approved for all sites if the process is documented in the protocol.
    - The NIH PI will submit the site-specific short forms in English and written summary of the consent along with the site-specific short form policies to the NIH IRB for review. This information may be included in the Local Context worksheet.
    - Each short form will include contact information for the NIH IRB and the Local PI contact.
- The NIH IRB will communicate the results of the translation review to the NIH PI, CC IRB Liaison, the local Site PIs(s), and the Institutional Designee(s)

Step 6: Study Closure—Responsibilities and Procedures

- Upon completion of the study at all sites, the NIH PI will submit relevant material for study closure to the NIH IRB according to NIH HRPP SOP 11A-Closure of an IRB-Approved Protocol (See Links).
- Per NIH policy, the NIH IRB will maintain records related to the protocol for at least 3 years after it is closed.

Step 7: Record Keeping—Responsibilities and Procedures

- Each Participating Site will maintain records of all human subjects research and related activities associated with a reliance agreement per the Participating Site's institutional

policies. Upon request, Participating Sites will provide a copy of such records to the NIH IRB.

- The NIH IRB will make IRB minutes and the IRB Rosters available to Participating Sites upon request. Requests must be made by the Institutional Designee.

LINKS

45 CFR 46.114: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.114

21 CFR 56.114:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.114

FDA information sheet: Non-Local IRB Review:
http://www.fda.gov/regulatoryinformation/guidances/ucm126423.htm

OHRP Guidance on Engagement of Institutions in Research:
http://www.fda.gov/regulatoryinformation/guidances/ucm126423.htm

FDA Guidance IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed:
http://www.fda.gov/regulatoryinformation/guidances/ucm366335.htm

NIH HRPP SOP 8, Procedures and Required Documentation for Submission and Initial Review of Protocols:
https://federation.nih.gov/ohsr/nih/ohrdocs/SOP_8_v4_2-4-16_508.pdf (NIH logon required)
http://ohsr.od.nih.gov/ohsr/public/SOP_8_v4_2-4-16_508.pdf (publicly accessible site)

NIH HRPP SOP 11A,Closure of an IRP-Approved Protocol:
https://federation.nih.gov/ohsr/nih/pnp.php (NIH logon required) or
http://ohsr.od.nih.gov/OHSR/pnppublic.php (publicly accessible site)

NIH HRPP SOP 16, Reporting Requirements for Unanticipated Problems, Adverse Events, Protocol Violations and Protocol Deviations:
https://federation.nih.gov/ohsr/nih/pnp.php (NIH logon required) or
http://ohsr.od.nih.gov/OHSR/pnppublic.php (publicly accessible site)

NIH HRPP SOP 16A, Allegations of Noncompliance with Requirements of the NIH Human Research Protection Program (HRPP):
https://federation.nih.gov/ohsr/nih/pnp.php (NIH logon required) or
http://ohsr.od.nih.gov/OHSR/pnppublic.php (publicly accessible site)

NIH HRPP SOP 20, NIH HRPP Requirements for Collaborative Research:
https://federation.nih.gov/ohsr/nih/pnp.php (NIH logon required) or
http://ohsr.od.nih.gov/OHSR/pnppublic.php (publicly accessible site)

NIH HRPP SOP 20A, Obtaining a Reliance (Authorization) Agreement at the NIH:
https://federation.nih.gov/ohsr/nih/pnp.php (NIH logon required) or
http://ohsr.od.nih.gov/OHSR/pnppublic.php (publicly accessible site)

NIH HRPP SOP 20B, NIH IRB Responsibilities When Reviewing Local Context Considerations for Offsite Research:
https://federation.nih.gov/ohsr/nih/pnp.php (NIH logon required) or
http://ohsr.od.nih.gov/OHSR/pnppublic.php (publicly accessible site)

NIH HRPP SOP 20C, Responsibilities when the NIH Intramural Research Program serves as a Coordinating Center for a Multisite trial or serves as the IRB of Record for a non-NIH Coordinating Center:

https://federation.nih.gov/ohsr/nih/pnp.php (NIH logon required) or
http://ohsr.od.nih.gov/OHSR/pnppublic.php (publicly accessible site)