IRB Member Tip Sheet: IRB Review When the NIH IRB is Reviewing Multi-Site Research

The NIH IRB typically serves as the Reviewing IRB in domestic multi-site (MS) studies when use of a single IRB (sIRB) is mandated by either the NIH sIRB Policy and/or the Cooperative Research mandate in the revised Common Rule. A key determinant is the funding source, specifically whether it is from the NIH or a different federal source.

When serving as the Reviewing IRB, NIH enters into a Reliance Agreement with Participating Sites (pSites) who will rely on the NIH for IRB oversight. The use of an sIRB is intended to streamline the review process by reducing delays, minimizing duplication, ensuring consistent implementation across sites, clarifying responsibilities, and strengthening participant protections while meeting federal and NIH policy requirements. An sIRB ensures one clear, consistent review, while still allowing sites to address their unique local context.

Multi-Site/ Cooperative Research	Involves more than one institution. Sites may be conducting identical activities or implementing different aspects of the same protocol.
Core Site (e.g., NIH study team)	The core site describes the lead study team, who has ultimate responsibility for the conduct and integrity of the research. They usually act as the main study point of contact for the Reviewing IRB, and they may serve as the conduit for communication with the pSites. The core site can also be referred to as the 'Lead Site' or 'Main Site'.
Participating Site (pSite)	A site involved in MS research that relies on the Reviewing IRB to provide regulatory oversight of the site. The Participating Site can also be referred to as the 'pSite', 'local site', or 'relying site'.
Reviewing IRB (NIH IRB)	The Reviewing IRB will be responsible for reviewing human subjects research and determining that the research meets the required criteria for approval under the applicable regulatory requirements. The Reviewing IRB can also be referred to as the 'single IRB', 'sIRB', 'IRB of record' or 'Central IRB.'
Reliance Agreement	Documents the use of the sIRB to review and approve the pSite's research activities. Outlines the authorities, roles, and responsibilities of the Reviewing IRB and participating institutions.

The NIH typically uses the Streamlined, Multisite, Accelerated Resources for Trials (SMART) Agreement v3.0 to document reliance arrangements. It is also known as the SMART IRB.

PROCESS FOR APPROVING NEW NIH MULTI-SITE (MS) PROTOCOLS

- **Two-Part Submission (Parent-Child Model):**
  1. The overall study and NIH (as the lead/core site) are reviewed and approved by the NIH IRB first.
  2. pSites are reviewed and approved later, after the study is approved, and a reliance agreement is in place with the specific site.
- **Submission Requirements:**
  - NIH submission resembles a single-site initial review but includes multi-site focused questions.
  - The study must be identified as "Multi-Site" in PROTECT to trigger multi-site questions and functions.
  - Includes model (e.g., study-wide template for consent or recruitment materials) and NIH site documents.
- **Protocol Characteristics (also see NIH protocol template):**
  - An MS protocol is less NIH-focused so that it can apply broadly to all sites.
  - Must describe study management across all sites.
  - Planned enrollment needs to be described (e.g., cumulative across sites or defined per site).
  - International research: NIH's role and the role of the international site(s) should be clearly delineated. International sites do not typically rely on the NIH IRB; best practice is for them to have local IRB or Research Ethics Committee review.

- **Study Materials:**
  - Include study wide model documents (e.g., consent forms, recruitment materials) that are reviewed and approved by the NIH IRB.
  - pSites adapt model documents to create site-specific versions before obtaining NIH IRB approval.
- **Financial Conflicts of Interest (pSites):**
  - If a financial conflict has been identified for any pSite investigator, the pSite provides a summary of the management plan to IRBO and this is passed on to the Protocol Royalties Analysis Committee (PRAC).
  - The PRAC will determine if further measures are needed to protect subjects, consistent with the reliance agreement.

Role of the IRBO (via Reliance Specialist and/or IRBO Analyst)

- *Initial Review:* Conduct a pre-review of the NIH protocol to ensure it is clearly written as an MS protocol and assess completeness and compliance with institutional policies and federal regulations.
- *After Protocol Approval:* Establish a Reliance Agreement with each pSite before they are added to the study.
- *Adding a pSite to the NIH Protocol:*
  - Review pSite documents (pSite protocol addendum, site specific consents etc.) and corresponding local context information.
  - Verify that the Relying Institution's HRPP has confirmed that the local context provided by the pSite is accurate and that their submission to the NIH complies with their local institutional requirements.

IRB Member Responsibilities

- **IRB Determination:**
  - NIH IRB determinations apply to the NIH and all relying sites.
  - Determinations for vulnerable populations (e.g., subpart D for children) and waivers of consent are made at the core (NIH) level and apply across all relying sites. This is applicable even if only one site is enrolling a vulnerable population.
  - The approval period for a protocol is determined at the core (NIH) level and applies to all sites regardless of when individual pSites are onboarded.
- **Review Responsibilities:**
  - Initial reviews, continuing reviews, and modifications of study-wide and/or pSite documents (protocol, model/site consents, recruitment materials, etc.)
- **Reportable New Information (RNI):**
  - RNIs are first reviewed by OHSRP leadership, then referred to the NIH IRB or Research Compliance Review Committee (RCRC), as applicable.
    - NIH IRB reviews potential unanticipated problems or information impacting subject decisions.
    - RCRC reviews potential serious or continuing noncompliance.
  - Both the NIH IRB and RCRC may:
    - Request additional information
    - Require modifications to protocol/consent(s)
    - Require subject notification
    - Increase safety monitoring or shorten review periods
    - Suspend/terminate IRB approval or enrollment if subject safety is at risk