

NIH Investigators and Multi-Site Research

INVESTIGATOR SEMINAR SERIES – February 12, 2024

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Learning Objectives

1. Introduction to the single IRB review of multi-site studies
2. Outline NIH Principal Investigator **responsibilities** when the NIH IRB serves as the Reviewing IRB
3. Identify **key considerations** when planning to submit a Multi-Site Study to the NIH IRB
4. Provide an **overview** of the initial submission process and **tips** to efficiently manage a Multi-Site Study when the NIH is the Lead Site and the Reviewing IRB

1. Introduction to the single IRB review of Multi-Site Studies at the NIH

- Key Terms
- Basic principles of single IRB review of multi-site studies

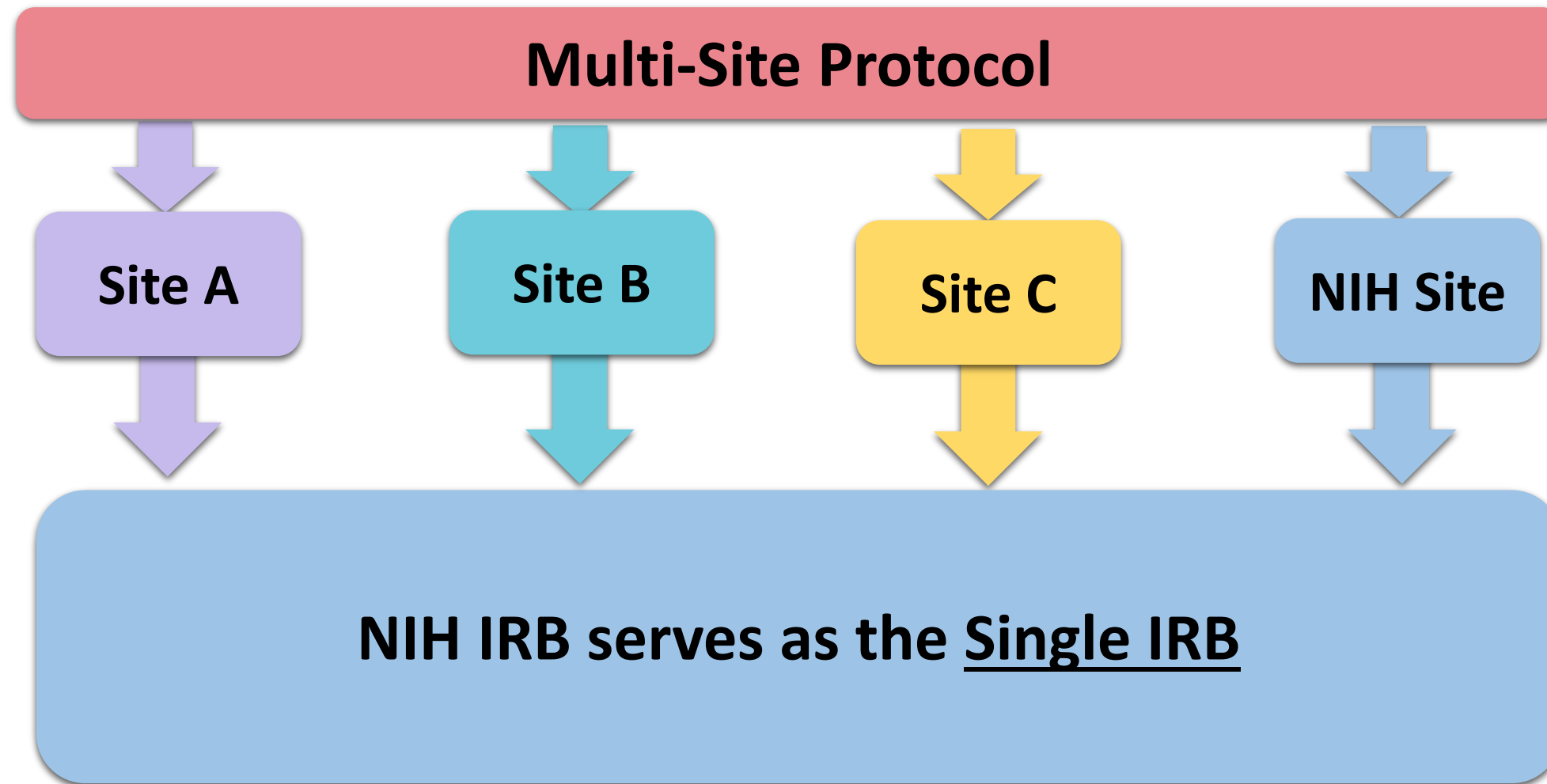
Key Terms when reviewing Multi-Site studies

TERMS	DEFINITION
Core Site	Term used to describe the lead study team. The core site has ultimate responsibility for the conduct and integrity of the research. It usually serves as the main study point of contact for the Reviewing IRB and may serve as the conduit for communication to and from the Participating Sites. The core site can also be referred to as the 'Lead Site' or 'Main Site.'
Participating Site (pSite)	A site involved in multi-site 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'.
Relying Institution	An institution participating in multi-site research that cedes IRB review to the Reviewing IRB for human subjects research consistent with the terms of a reliance agreement. The Relying Institution may involve more than one participating study site, e.g., one healthcare system may have multiple hospitals and/or clinics.
Reviewing 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 regulatory requirements at 45 CFR 46 and, as applicable, 21 CFR 50; 312; 812. When reviewing for a multi-site study, the Reviewing IRB can also be referred to as the 'single IRB (sIRB),' 'IRB of record' or 'Central IRB.'

Principles of single IRB review of multi-site studies*

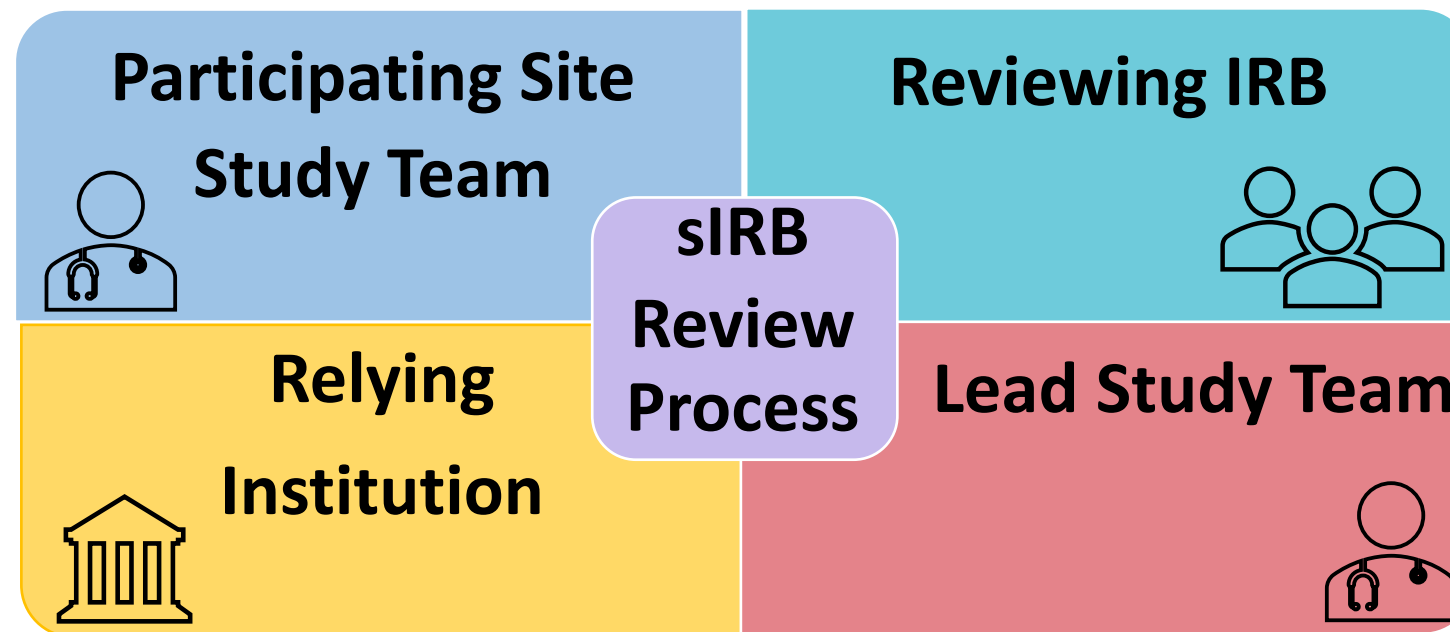
- **Multi-Site research** involves more than one institution in human subjects research
 - Sites may be conducting identical activities or implementing different aspects of the same protocol
- **Single IRB (sIRB) review** occurs when an individual IRB reviews and approves research for all pSites involved in a multi-site protocol instead of each site obtaining individual approvals
 - Streamlines the IRB review process for study teams, institutions, sponsors and IRBs
 - Allows research to proceed expeditiously without compromising on ethical principles, human research protections, and IRB review quality
 - May become aware of study-wide safety issues sooner
- **Single IRB (sIRB)** also known as the Reviewing IRB, IRB of Record, or Central IRB
- **Different**, not necessarily **less** work for all involved
- **Reliance Agreements** are used to document the use of the sIRB to review and approve the Participating Site's research activities

Single IRB review of multi-site studies



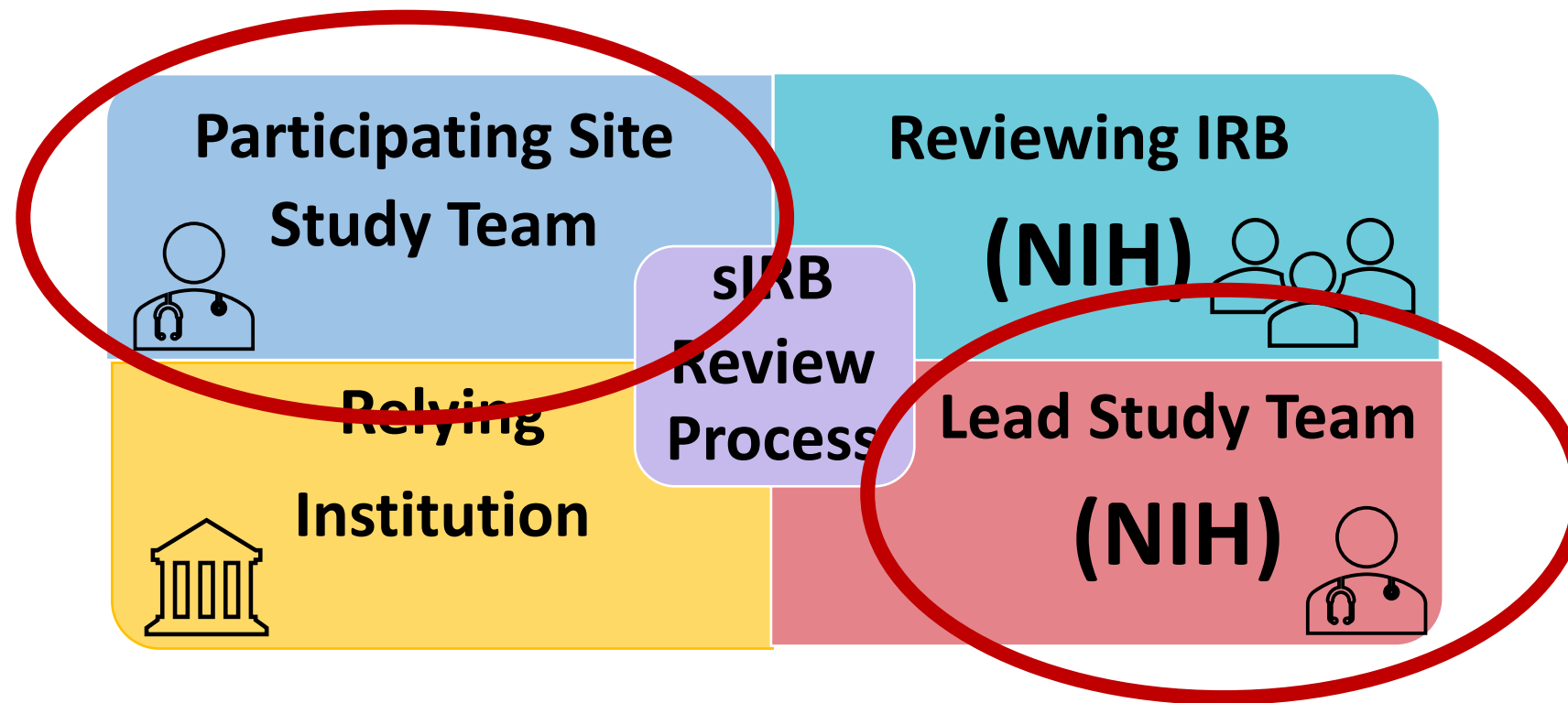
Single IRB review of multi-site studies

- Use of a single IRB was **mandated** by **NIH** on Jan 25, 2018, and by the new **Common Rule** on January 20, 2020
- **Mandates** depend on whether multi-site studies are NIH and/or Federally-funded
- sIRB review involves **4 key players**, and to be successful, each player must know their role and responsibilities



2. Investigator Responsibilities

- NIH Principal Investigator (PI) Responsibilities
- Participating Site Principal Investigator (PI) Responsibilities



NIH PI Responsibilities for a Multi-Site Study

- Overall responsibility for the entire study
- Ensures protocol and other study documents are submitted to NIH IRB
- Confirms all approvals, IRB and ancillary, are obtained prior to the study beginning or implementing modifications
- Makes sure events are reported to the NIH IRB per NIH HRPP Policy 801 and Federal requirements
- Conducts the study per:
 - The current IRB approved protocol, consent form(s), etc.
 - NIH policies and Federal requirements

NIH PI Responsibilities for a Multi-Site Study

- Make sure pSites know about the NIH's IRB processes, requirements and policies e.g., reporting requirements
- Guarantees all pSites have current versions of all IRB-approved documents
 - Facilitated via PROTECT - NIH PI still responsible to ensure sites have awareness and access to materials
- Ensures all pSites conduct the study per the approved protocol
- Submits **Initial** (onboarding) site materials and **Continuing Review** form to the NIH IRB for all pSites (required by PROTECT eIRB workflow)
 - Note: pSite **Modifications** are submitted by the pSite PI, but the NIH PI should be aware of any pSite mods being submitted

pSite PI Responsibilities for a Multi-Site Study

- Oversees all aspects of the study at the pSite
- Reviews and follows policies/procedures of the NIH IRB e.g., reportable events requirements; how personnel updates are handled
- Understands the role of their local HRPP/IRB office when ceding to an external IRB
- Secures all ancillary approvals from home institution
- Provides the NIH IRB with appropriate local information e.g., accurate pSite addendum, and tailors the pSite consent e.g., contact information, local injury language, by using the NIH IRB approve model consent form template
- Ensures both the reliance is in place & IRB approval secured before beginning the study at their local institution
- Conducts the study per:
 - The current IRB approved protocol, consent form(s), etc.
 - NIH policies, Federal requirements, and applicable local requirements

pSite PI Responsibilities for a Multi-Site Study

- Ensures all pSite modifications are submitted and approved prior to implementing the changes
- Provides the Lead Study Team information about study progress for continuing review
- Ensures events that occur at the local institution are reported to the NIH IRB per NIH HRPP Policy 801 and federal requirements
 - Most likely will have dual reporting requirements
- Communicating with or obtaining authorization from their local institutions when needed e.g., from SMART IRB Point of Contact in the case of site PI change, COI updates, changes that may be affected by state law or institutional requirements

3. Key considerations when planning to submit a Multi-Site Study to the NIH

- Confirm use of the NIH IRB
- Set Up Guard Rails
- Site Selection
- Development of Protocol and Consent Documents

Key Considerations

Confirm use of the NIH IRB

- If NIH is the lead institution, NIH IRB will usually serve as the sIRB
- Consulting with IRBO is required if:
 - New study includes 6 or more pSites
 - Proposed pSite is DoD, Federal agency, and/or International
 - Existing multi-site study plans to add 5 or more enrolling sites
- Is the NIH IRB the appropriate to serve as the reviewing sIRB?

Set Up Guard Rails

- Secure regulatory support e.g., Protocol Navigator/ Study Coordinator
- Learn about the NIH IRB's submission requirements
- Develop a communication plan e.g., site initiation meetings; conference calls; newsletter; email blasts; training materials
- Decide whether NIH will be the coordinating center
- Educate pSites e.g., PROTECT system, submission process

Key Considerations

Site Selection

- Identify a Site PI and a regulatory contact who will support that PI
- Assess their research experience and bandwidth to participate – are they able to serve as a pSite?
- Confirm Site PI knows their local HRPP/ IRB's role and requirements
 - Are they signatories to the SMART IRB Agreement?
 - Do they need to submit a shadow protocol to their local IRB?
 - Are they ok with relying on the NIH IRB?
- Establish whether pSite decisions/ reviews are contingent on pSite funding
- Critically consider local context issues - learn about how they will implement the protocol e.g., what is considered clinical care at the site
- Confirm location – will research protocol be implemented across multiple local sites? Are they within the same institution?

Key Considerations

Development of Protocol and Consent Documents

- NIH team creates NIH documents as well as **model templates** for consent forms, recruitment materials, and other documents that pSites will use
- Distinguish between study-wide documents **vs** NIH-site **vs** pSite documents
- Harmonize as much as possible in the model documents
 - Consider how it will scale up over many sites?
 - Allow for customizations based on law or policy and **limit** when they are not
 - Identifying local study team and points of contact
 - HIPAA
 - Research-related injury language
 - Conflicts of Interest
- Be mindful that other sites are not Federal entities or research institutions
- Be flexible when you can and it makes sense
- Effectively manage expectations, timelines, resources and site selection

Key Considerations

Development of Protocol and Consent Documents

- Protocol includes study-wide information so the NIH IRB can review and approve
 - Make the protocol as general as possible and applicable study-wide
 - Carve out NIH-specific differences – consider creating an NIH addendum – but when this is done, indicate how pSites will handle the equivalent in a general way
 - pSite differences can be captured in the **pSite addendum** (discussed later)
- Avoid confusing sites and inadvertently causing deviations if the information is not general enough to apply to all sites or documented as applicable only to NIH
 - **Example:** Going into detail about how NIH assesses Adults who Lack Capacity to Consent, but not addressing, even generally, how other sites will handle it

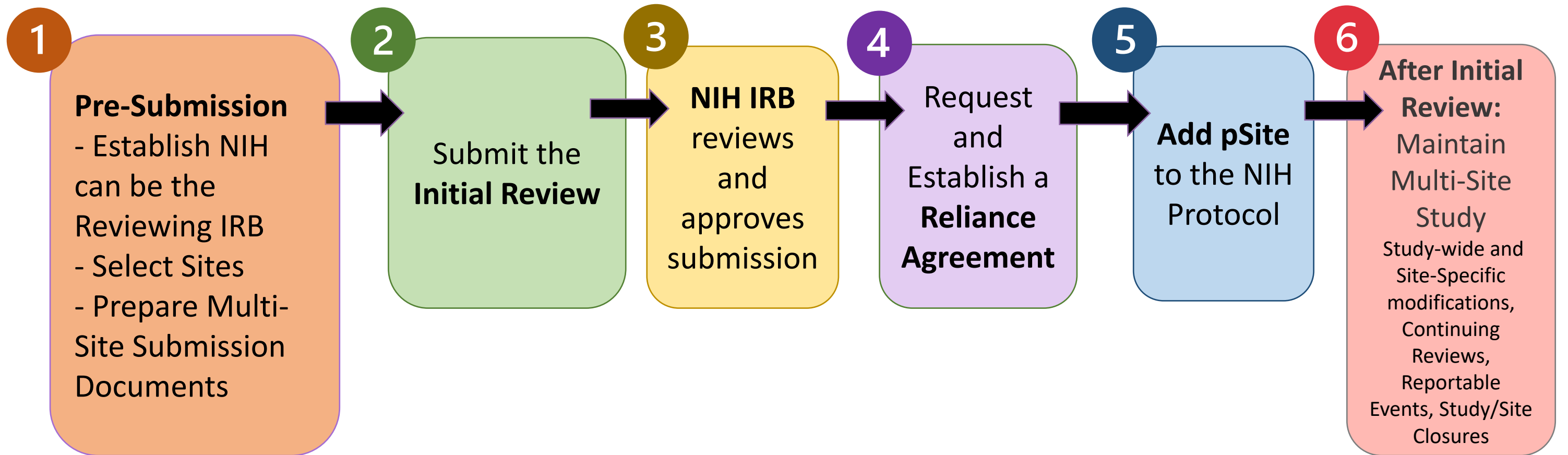
4. Submission and Maintenance Strategies

- Overview of NIH review process of multi-site studies
 - *New* multi-site study and adding pSites
 - Converting existing single-site study to multi-site
- Putting a Reliance Agreement in place
- pSite Submission Process
- Amendments/Modifications and Continuing Review

Process for Approving *NEW* NIH Multi-Site Protocol and adding a pSite

- Two-part submission process (Parent-Child Model)
 - NIH, as the lead site, and overall study approved first
 - pSites are reviewed **after** the protocol is approved and a Reliance Agreement is in place
- NIH submission is like a Single Site Initial Review submission
 - Not many differences in this regard except questions asked in PROTECT that are specific to multi-site
 - Study needs to be identified as “Multi-Site” in PROTECT to trigger branching questions and multi-site functions
 - Includes model templates (study-wide) and NIH site documents

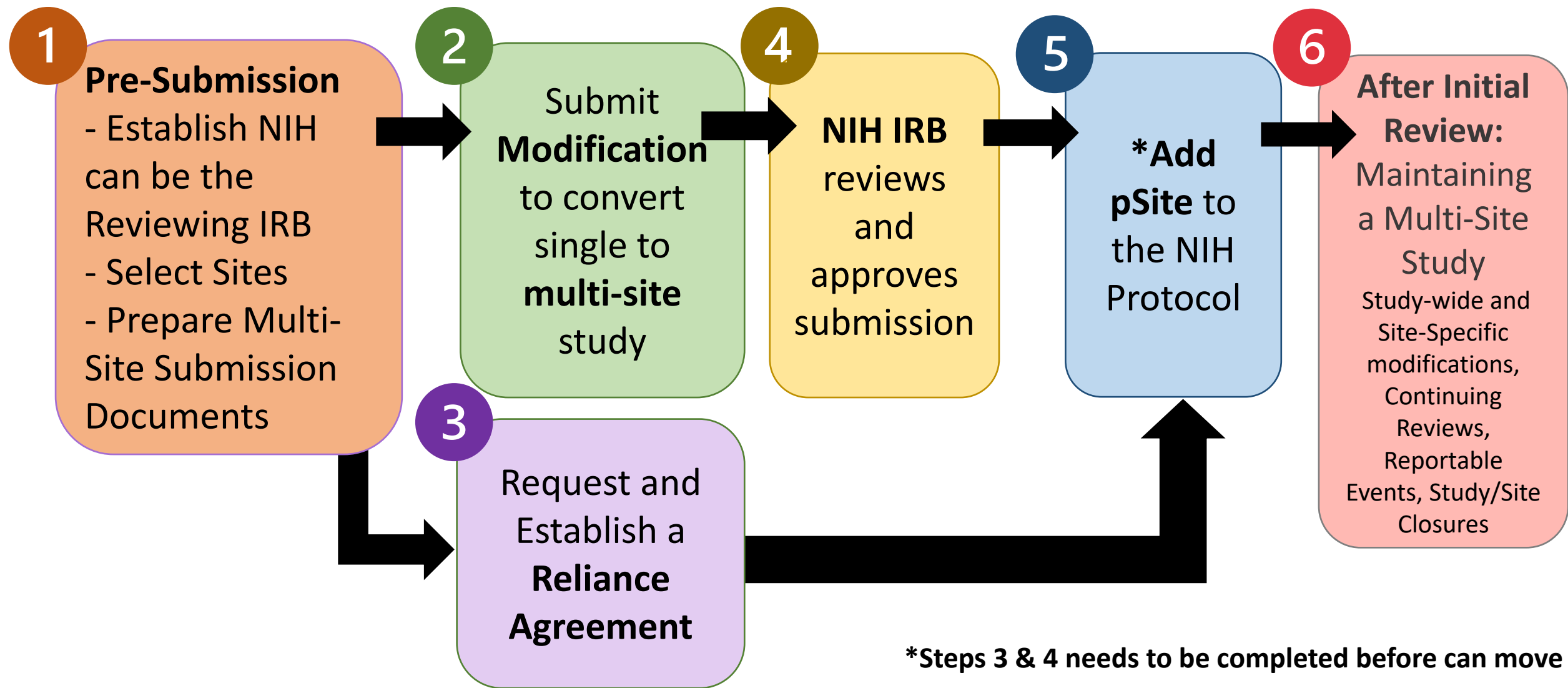
Process for Approving *NEW* NIH Multi-Site Protocol and adding a pSite



Process for **CONVERTING** Existing NIH Protocol to Multi-Site and adding a pSite

- A Modification in PROTECT is required to convert an approved single-site study to a multi-site study when the NIH IRB will serve as the sIRB
 - This will trigger the multi-site branching questions and functions in PROTECT
- Protocol may need to be revised to accommodate change – *guidance to follow*
- Model consents and/or model recruitment materials should be developed and included in the submission
- pSites are reviewed and approved **after** the modification to convert the study to multi-site is approved and a Reliance Agreement is in place

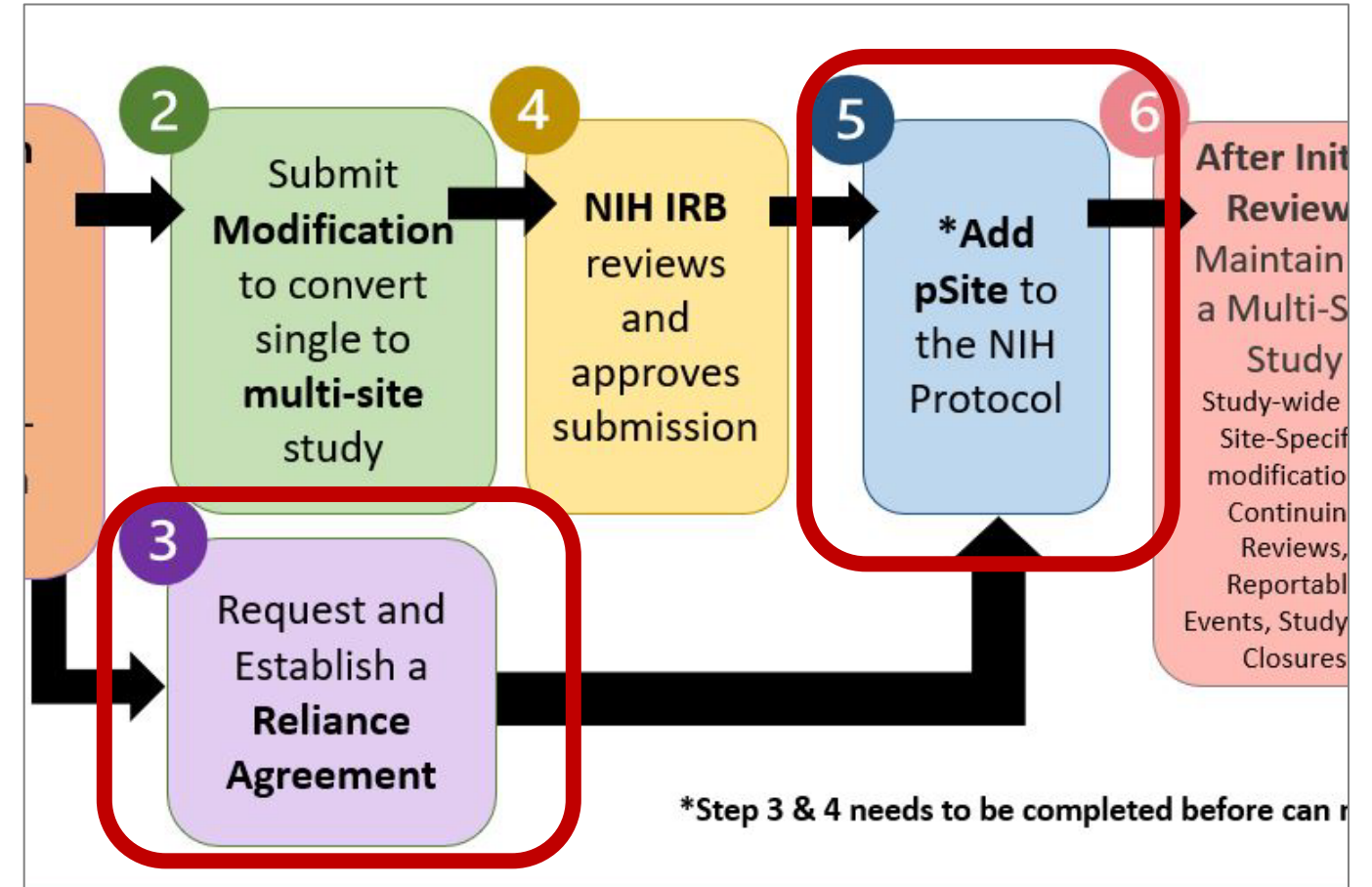
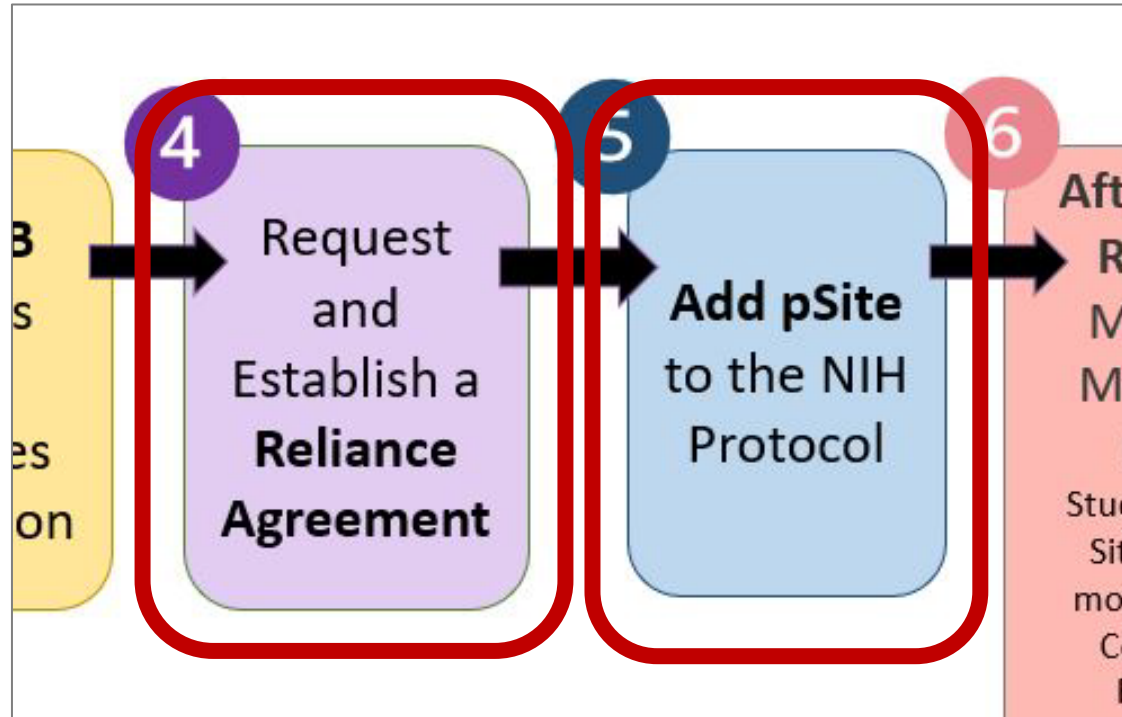
Process for *CONVERTING* Existing NIH Protocol to Multi-Site and adding a pSite



*Steps 3 & 4 needs to be completed before can move to Step 5

Reliance Agreements

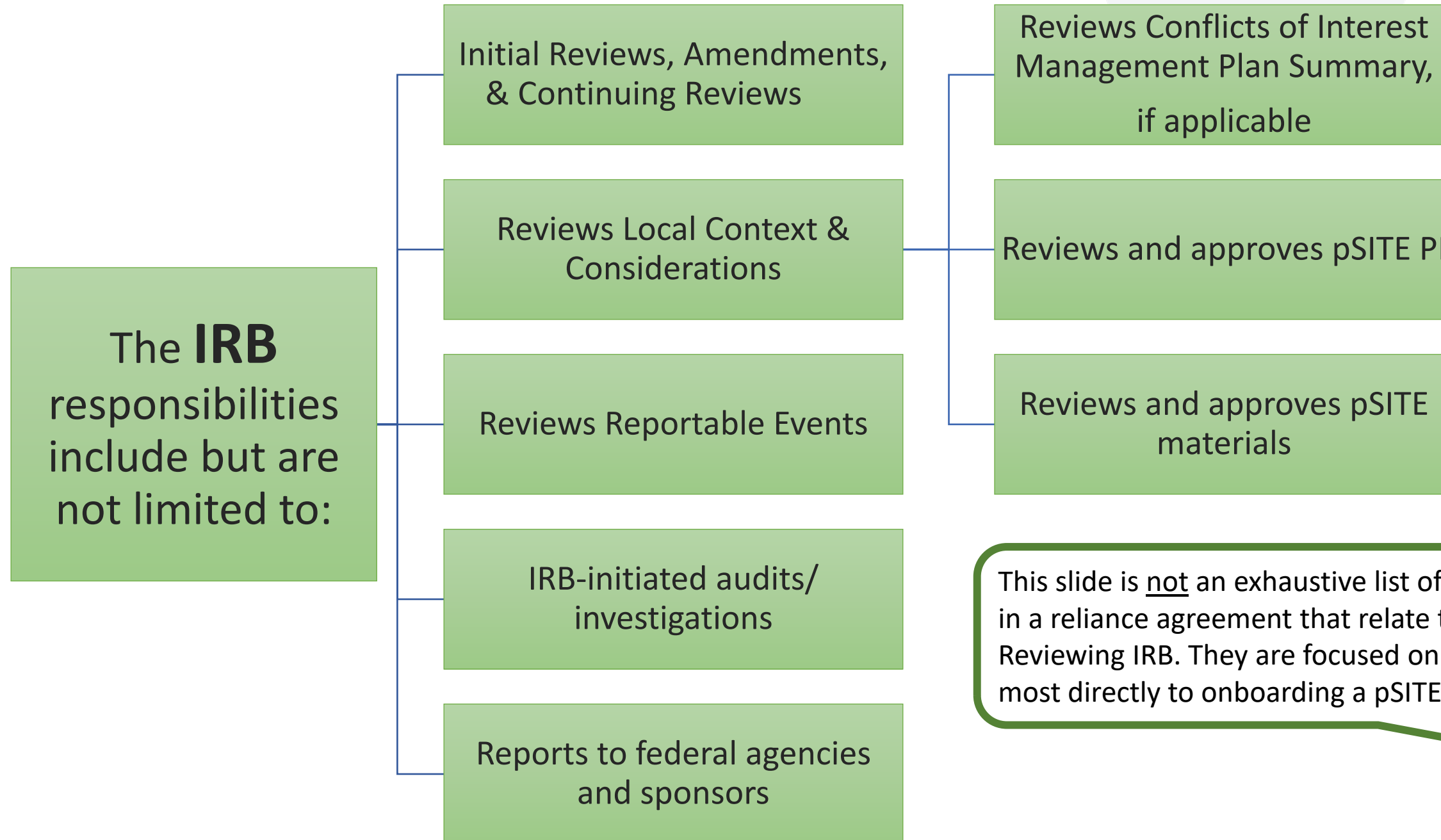
Add a Participating Site



Reliance Agreements

- Written agreement between the **Reviewing IRB Institution** and the **Relying Institution (Participating Site)**
- Documents the use of the Reviewing IRB to **review** and **approve** the Participating Site's research activities
- Delineates the institutions responsibilities for reviewing the research
 - Some of these are delegated to the NIH and/or pSite study team
- Content is generally consistent, but scope can vary
 - Master Agreement with SMART IRB – *more later*
 - Regular NIH template for a single protocol
- **Only** NIH OHSRP is authorized to execute a reliance
- Reliance Agreement is typically established *BEFORE* the pSite is added

Reliance – NIH IRB Responsibilities



This slide is not an exhaustive list of all the clauses in a reliance agreement that relate to the Reviewing IRB. They are focused on what relates most directly to onboarding a pSITE.

Reliance – pSite Responsibilities

pSITE
responsibilities
include but are
not limited to:

Providing pSITE-specific protocol and consent documents, recruitment materials, etc.

Notifying Reviewing IRB of reportable events according to NIH IRB policies

Providing Local Context
State/ local laws and regulations, institutional requirements, local factors

Providing Documentation/ Assurances
pSITE study team appropriate qualifications & training, local HRPP confirms local context accurate

Communicates findings from ancillary reviews that impact risk/ benefit

Provides the Reviewing IRB with information about local study conduct that differs from approved protocol

Reviews and approves study personnel

Provides Conflicts of Interest management plan summary, if applicable

This slide is not an exhaustive list of all the clauses in a reliance agreement that relate to the pSITE. They focus on what relates most directly to onboarding a pSITE.

The *process* of putting a Reliance Agreement in place at the NIH

- 1** The NIH PI/designee submits a [Reliance Request Form](#) – link on IRBO website
 - Notifies IRBO of request for NIH to rely on an external IRB
- 2** Sends a copy of the protocol to NIH-Reliance-sIRB@nih.gov
 - It should be the **approved** protocol or final draft that will be submitted for initial review
- 3** The Reliance Specialist processes the request and works with the external institution to execute the agreement
- 4** Typically, one of the following is used to document a reliance arrangement:
 - The [SMART Agreement](#)
 - An existing Programwide Reliance Agreement
 - The reviewing IRB's Reliance Agreement template
- 5** The Reliance Specialist notifies the NIH study team when the reliance is in place
 - When NIH is the IRB, the Reliance Specialist creates the Participating Site shell in PROTECT

SMART IRB

- SMART IRB is a “Master” reliance agreement with 2 versions - not an IRB
- NIH is only permitted to rely on, or be relied upon by another v. 2 signatory
- Its use is documented on a study-by-study basis via online platform or letter
 - NIH study teams are advised by IRBO **if/ when** to use the online platform
- Submissions using SMART need to be *strategic* due to the systems’ functionality

EXAMPLE: If setting up a 10-site study with all SMART signatories, NIH needs to be thoughtful about when the reliance request is issued to those sites as NIH cannot send additional requests until the original recipients come back with a decision to rely or not

Tips for putting a Reliance Agreement in place at the NIH

TIMELY not EARLY SUBMISSIONS

- Submit when the protocol is approved or very close to being approved
 - Approval means there is clarity about the sites, their research role and templates
 - Generally, aligns better with the external institution's processes (as sIRB or pSite)
- Submit when confident that sites will be involved in the NIH study

MISALIGNED RELIANCE WORKFLOWS

- Find out the external IRB's reliance process and incorporate that into your plan
- Tell potential pSites about the NIH IRB multi-site processes e.g., PROTECT account

ADDITIONAL REQUIREMENTS FROM THE HRPP/ IRB

- Ask pSites to find out about their local processes and identify what they need from the NIH

NIH is the Reviewing IRB: Adding a pSite to the Protocol

- A pSite is added to the protocol **AFTER** the Reliance Agreement is in place
- Only possible if in PROTECT:
 - Study is identified as **multi-site** as this activates multi-site functions
 - pSite Institution has an ***Institutional Profile***
 - pSite PI has a PROTECT account } Request via a PROTECT Help Desk Ticket
- The Reliance Specialist creates a shell for the future submission of pSite documents to the NIH IRB when the reliance is in place
- The **creation** of the pSite shell in PROTECT is **NOT equivalent** to an **IRB approval** of the pSite
- NIH team serves as a gatekeeper before pSite documents are submitted
- Move from “**Awaiting Site Materials**” to “**Pre-Review**”

NIH is the Reviewing IRB: Adding a pSite to the Protocol

1

ID	Name	SmartForm Institution	Principal Investigator	State	FWA Number
SITE000140	Childrens Healthcare of Atlanta Participating Site for The CAR-CURE Trial	Childrens Healthcare of Atlanta	Muna Qayed	Pre-Review	00000644
SITE000116	Childrens Hospital Los Angeles Participating Site for The CAR-CURE Trial	Childrens Hospital Los Angeles	Emily Hsieh	Active	00001914

2

IRB > The CAR-CURE Trial > Dana Farber Cancer Institute Participating Site for The CAR-CURE Trial

Awaiting Site Materials

Last updated: 8/14/2023 1:40 PM

Next Steps

- Edit Site
- Printer Version
- Submit Site Materials
- Assign Coordinator
- Assign Primary Contact
- Assign PI Proxy

SITE000117: Dana Farber Cancer Institute Participating Site CAR-CURE Trial

Principal investigator: Francesca Alvarez-Calderon
Submission type: IRB Site
Primary contact: Anna Lyczmanenko
PI proxies:
Institution: Dana Farber Cancer Institute

IRB office: NIH IRB
IRB coordinator: Shirley Rojas
Regulatory authority: 2018 Requirements + FDA
Study: 000792

Link to PQS/OPS.

3

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graph LR; A[Invitation Pending] --> B[Awaiting Site Materials]; B --> C[Pre-Review]; C --> D[IRB Review]; D --> E[Post-Review]; E --> F[Review Complete]; E --> G[Modifications Required]; G --> D;
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NIH is the Reviewing IRB: Adding a pSite to the Protocol

- NIH IRB reviews the pSite PI and pSite documents
 - Expectation that the pSite will review pSite study team per local requirements
- pSite submissions are typically reviewed as expedited actions
- Includes:

<input checked="" type="checkbox"/> pSite Protocol Addendum (use IRBO template)	<input checked="" type="checkbox"/> pSite Recruitment materials (if applicable)
<input checked="" type="checkbox"/> pSite Consents/ Assents (if applicable)	<input checked="" type="checkbox"/> pSite HRPP Clearance (via letter or email)
- **pSite Protocol Addendum:** Supplements the pSite Application in PROTECT; provides important information about local context and protocol implementation
- **pSite HRPP Clearance:** Provides confirmation that pSite's institutional requirements are met and local context provided has been vetted by the pSite HRPP/IRB office

Tips when adding a pSite to the Protocol

- Request PROTECT accounts for the pSite users when submitting the reliance request
- Factor in the time/effort for the pSite to complete pSite requirements
 - Home Institution requirements e.g., ancillary reviews, Col, reliance request etc.
 - Creation of site documents based off NIH model templates
 - Consider their resources – Is the pSite PI primarily a clinician? Reg support?
- NIH teams should lean into their gatekeeping role
 - NIH and pSite should partner in developing pSite materials
 - NIH team should critical review the pSite submission
 - Try to anticipate issues that the NIH IRB may identify
- Ensure the pSite submission includes local context information
 - Check the pSite has completed site documents based off NIH model templates

Maintaining a Multi-site Study post-Approval (MODs/CRs/Closures): Study-wide and Site-specific Considerations

NIH Study Team:

- Submits **Study-Wide** Modifications, Continuing Reviews (CR)*, Event Reports (both NIH site reportable events and pSite reportable events), and Closures
- Ensures protocol compliance and safety monitoring
- Serves as the key liaison between the NIH IRB and Participating Sites

pSites:

- Submit **site-specific** Modifications, Continuing Review* information, Site-Specific Event Reports, and Site-Specific Closures

**REMINDER: pSites report site CR data in PROTECT to the NIH team. The NIH Team submits a CR that encompasses the entire study incorporating that data.*

Tips for Maintaining a Multi-site Study – MODs/CRs

Modifications:

- Communicate in advance and plan with pSites when study-wide amendments will require pSites to modify their documents
- Factor in the time it can take to approve a study-wide amendment and the subsequent pSite amendments e.g., model ICFs, then pSite ICFs
- Consider reconsenting timeframes, as well as consenting new subjects
- pSites submitting site specific modifications – need for communication outside of PROTECT

Continuing Reviews:

- Communication between the NIH and pSite study teams is key to getting accurate and timely data submitted prior to the NIH study team submitting the study-wide CR
- Closures:
 - A pSite can only close when all closure criteria are met for the site, including analysis of identifiable data at the site
 - Overall study closure cannot occur before pSites are formally closed in PROTECT

NIH and Site-specific Reportable Events

- The NIH PI, as part of the Lead Site, is responsible for ensuring that all reportable events are provided to the NIH IRB per [NIH HRPP Policy 801](#) , including the pSITEs
 - However, pSites PIs are also responsible for ensuring reportable events that occur at *their* site are reported to the NIH IRB
- Reportable New Information (RNI) forms can be submitted by any PROTECT user
- Information on how to submit a reportable event i.e., **Reportable New Information**, can be found in the [PROTECT: NIH is the Single IRB of Record Guide](#)

Tips for Maintaining a Multi-site Study – RNIs

Reportable Events/ Reportable New Information:

- Communication between the NIH and pSite Study Teams is key for RNIs to be submitted efficiently and accurately
 - When a pSite PI submits an RNI directly to the IRB, PROTECT does not send the NIH PI a notification
 - pSITE PI therefore needs to separately notify the NIH PI.
 - The NIH PI can view the RNI in PROTECT but cannot edit or progress with the RNI
 - The submitter of the RNI 'owns' it and is the only one who can edit it, etc.
- Reminder: pSites need to be aware of dual reporting requirements i.e., needing to report events to both the NIH IRB and their home institution.

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Additional Resources

1. [What You Need to Know About Single IRB Review: Principles and Practice \(Part 1\)](#)
– OHSRP Education Series, July 7, 2020
2. [What You Need to Know About Single IRB Review: Principles and Practice \(Part 2\)](#)
– OHSRP Education Series, August 4, 2020
3. [Overview: NIH Multi-Site Protocol Processes](#) - Protocol Navigator Meeting, July 14, 2022
4. [The Single IRB Model at the NIH: Principles, Processes, and Pitfalls](#) - OHSRP Education Series, November 2, 2023
5. [NIH Protect Help Center](#)

Contact Us

NIH IRB Reliance & sIRB Team

For further guidance or questions:

Web: [Reliance and sIRB IRBO webpage](#)

Email: NIH-Reliance-sIRB@nih.gov



Questions?

