The Single IRB Model at the NIH: Principles, Processes, and Pitfalls

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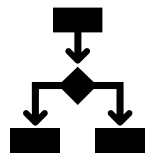Reliance Specialist, Office of IRB Operations (IRBO)

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Learning Objectives

Principles

Provide a refresher on Single Institutional Review Board (sIRB) review principles

Processes

Describe current processes for NIH study teams when:

- NIH is the Reviewing IRB
- NIH is relying on an External IRB

Pitfalls

Discuss best practices for avoiding common pitfalls when working with an sIRB

Previous OHSRP Education Sessions

1. [What You Need to Know About Single IRB Review: Principles and Practice (Part 1)](#) – July 7, 2020

2. [What You Need to Know About Single IRB Review: Principles and Practice (Part 2)](#) – August 4, 2020

3. [Overview: NIH Multi-Site Protocol Processes](#) - Protocol Navigator Meeting, July 14, 2022

Key Terms

| TERM	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 serves 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	A research site involved in multi-site research that relies on the Reviewing IRB to provide oversight for 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 then 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.'

NIH can function as one or a combination of these designations.

PART 1:

NIH IRB serves as the reviewing single IRB for a multi-site protocol
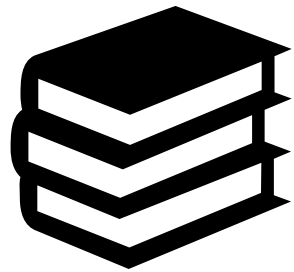
Principles
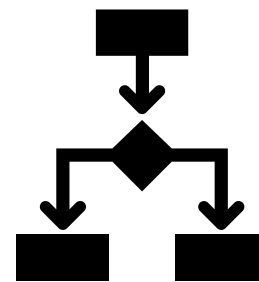
Processes

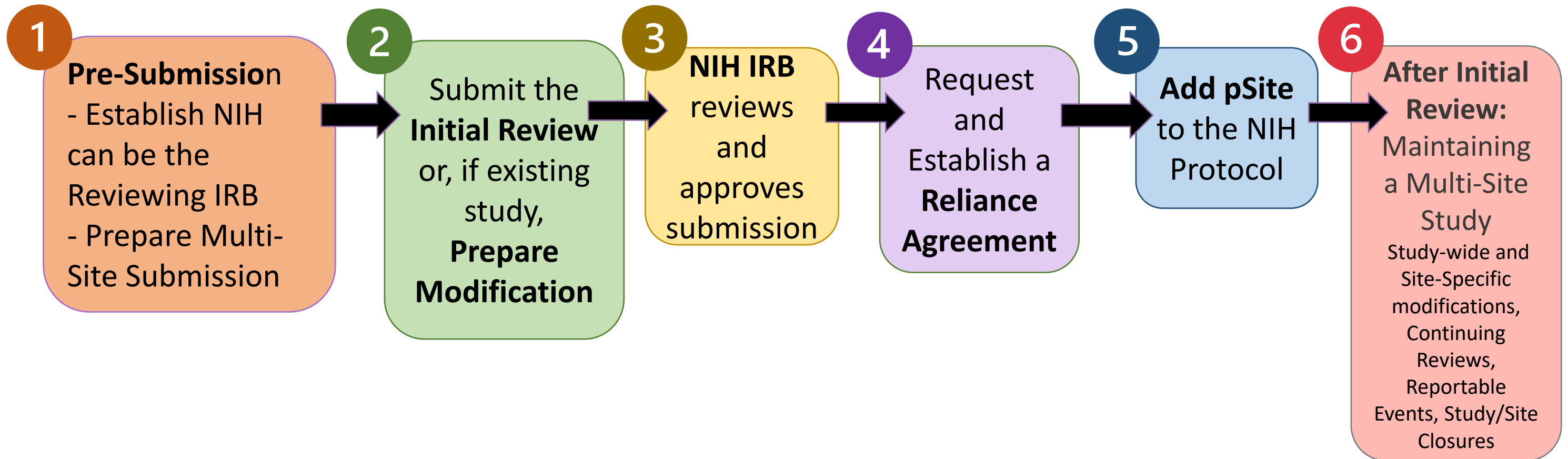**Pitfalls**

Principles of NIH Single IRB Review

- Single IRB (sIRB), also known as the Reviewing IRB, IRB of Record, or Central IRB

- One IRB reviews and approves research for all participating sites (pSites) involved in a multi-site protocol

  - Same charge: sIRB reviews multi-site protocols to ensure compliance with local, state, and federal laws, as well as NIH policies

    - Also factor in local context at pSites

- Reduces administrative burden, increases efficiencies, and provide consistent human subjects protections

  - Allows research to proceed expeditiously without compromising ethical principles, human research protections, and IRB review quality

  - May be aware of safety issues study-wide sooner

  - **Different**, not necessarily **less** work for all involved

Process for Approving the NIH Multi-Site Protocol and adding a Participating Site

This diagram illustrates the process for **NEW/EXISTING** multi-site protocols submitting to the NIH IRB with a plan to add new sites

1 **Pre-Submission**
- Establish NIH can be the Reviewing IRB
- Prepare Multi-Site Submission

2 Submit the **Initial Review** or, if existing study, **Prepare Modification**

3 **NIH IRB** reviews and approves submission

4 Request and Establish a **Reliance Agreement**

5 **Add pSite** to the NIH Protocol

6 **After Initial Review:** Maintaining a Multi-Site Study Study-wide and Site-Specific modifications, Continuing Reviews, Reportable Events, Study/Site Closures

Process

1 Pre-Submission: Establish that NIH can serve as the Reviewing sIRB

- Is the NIH IRB the appropriate to serve as the reviewing sIRB?
- If NIH is the lead institution, NIH IRB will usually serve as the sIRB
  - A consultation with IRBO's Reliance/sIRB team (meeting or email) is needed for the following:
    - New study includes Six (6) or more Participating Sites (pSites), in addition to the NIH site
    - Existing multi-site study adding five (5) or more enrolling sites
    - Involves Department of Defense (DoD); and/or other Federal Agency sites; International study requesting that the NIH IRB be the reviewing IRB for those sites
  - Email sent confirming decision that the NIH IRB can serve as the sIRB
  - Consult not required with our office if a new multi-site study only includes NIH plus a maximum of a five (5) pSites or existing multi-site study is adding four (4) or less sites
  - Consultation OK if the above scenarios do not apply **OR** for any questions or concerns prior to NIH serving as the sIRB

1 **_Potential Pitfalls_** when establishing that NIH can serve as the Reviewing IRB

- Failure to consult with the NIH Reliance/sIRB team when required
    - Can cause a delay in the study startup

- Study team not having enough information re: the study
    - Unknown number of sites, NIH PI not assessing capacity to assume lead site/coordinating center functions, not considering the number of consent/assent forms

- NIH study team not confirming that all pSites are willing/able to be participate in the study
    - While sIRB mandates leave limited discretion in opting out of sIRB review, it is important to verify that a potential site is willing and capable of serving as a pSite

- PIs/Study Teams new to leading or participating in a multi-site protocol forgo meeting with the NIH Reliance/sIRB team to resolve any questions/issues upfront to avoid delays

Pre-Submission: Preparing the IR Multi-Site Submission

- NIH, as the Lead Site and/or Coordinating Center, creates the protocol
  - Includes overall study information so the NIH IRB can appropriately review and approve the study
    - Will be used by all pSites, so it must apply study-wide
  - Make the protocol as general as possible.
    - NIH-specific differences need to be delineated or carved out
      - Consider creating an NIH addendum or an appendix within the protocol to separate the NIH specific information from study-wide information)
  - pSite differences will be captured in the pSite addendum (discussed later)
- NIH study team creates model templates for consent forms, recruitment materials, and other documents that pSites will use
    - The NIH specific documents are also developed during this time

Potential Pitfalls when preparing a Multi-Site Submission

- Not managing the NIH specific information in the protocol
  - Could confuse sites and inadvertently cause deviations if the information is not general enough to apply to all sites or documented as applicable only to NIH
  - If the protocol includes specific information about how the NIH will handle something, it should also include, at a minimum, general information about how other sites handle it, if applicable
    - Example: Going into detail on how NIH assesses Adults who Lack Capacity to Consent, but not addressing, even generally, how other sites will handle it
- Not preparing adequate model template materials
- Lead Study Team not considering its role in serving as a coordinating center, when applicable

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Potential Pitfalls when preparing a Multi-Site Submission – Coordinating Center

- Not one definitive definition of a Coordinating Center
- The term 'Coordinating Center' can cover several very different research-related activities
  - Can be the NIH PI/Lead Site or delegated to another entity
  - Some only handle data center functions
  - Some have study-wide responsibilities of most or all aspects of the multi-site protocol e.g., consent form development, coordinate data collection, create and manage the overall operations of a study
  - Contract and/or grant should outline scope of work to outline Coordinating Center activities and those of the pSITE(s)
- Coordinating Center functions need to be clearly described in the protocol

Submitting the Initial Review

- Two-part submission process (NIH Site and pSites)
  - pSites are reviewed after the NIH, as the lead site, is approved
    - Not all IRBs follow this model/ some approve Lead/pSites at once

  - NIH Site 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

Submitting a Modification to convert Single Study to Multi-Site

- 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 is revised per guidelines previously discussed

- Model consents and/or model recruitment materials are developed

- The modification must be approved prior to any pSite being reviewed and approved

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Potential Pitfalls when submitting an Initial Review or Modification

- **Initial Review:**
  - Not submitting all applicable model documents or submitting inadequate versions
  - Not developing a general enough protocol to apply to all sites
  - Not managing expectations on when pSites will be reviewed and approved
    - Ensure all sites are aware that NIH follows a 2-step process (NIH site approved first, followed by pSites)
- **Modification to Convert:**
  - Not revising the protocol to adequately serve as a multi-site protocol
  - Not developing good model documents, specifically consent forms
    - Best to use the model ICF template as reference when NIH is the lead site vs only using the existing NIH consent as a reference
- **IRs/MODs**: Not working with relying sites to consider any issues that may hinder conducting the protocol
  - NIH Study Team should critically consider any local context issues
  - Will sites be able to comply with NIH IRB policies?

3

NIH IRB Reviews and Approves the New Study or Modification

- NIH IRB reviews the Initial Review submission per its regular process
  - Main differences are the content of the protocol and study-wide documents, especially the model ICFs

- NIH IRB will review and approve:
  - Main Protocol
  - Model documents (consent; recruitment material)
  - NIH site-specific documents
  - Communication Plan, if available
  - Consent waiver requests
  - Other study documents

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3

- Protocol does not adequately document the study as a multi-site study
  - Possibly too NIH specific/ not general enough
  - Does not include all vulnerable populations for the IRB to make a determination
    - For example, if only one pSite is enrolling children, the IRB needs to make that determination with the IR, not when that pSITE submits its materials for approval

- Model template documents are not submitted

- Model template documents are not generic enough or do not contain placeholders for sites to insert their local information

- Many of these issues will be addressed during the IRB pre-review by analysts. However, it can still hold up a review and potentially lead to a deferral by the IRB if not addressed.

3 **Potential Pitfalls** when the NIH IRB Reviews and Approves
the New Study or Modification - Communication Plan

- NIH PI/Lead Site and pSites communicate differently in PROTECT than in iRIS
  - Not a way to send correspondence within PROTECT to each site
    - Cannot rely solely on the eIRB system to facilitate communication across sites

  - Consider differences when developing/ executing a communication plan

  - Suggest NIH Study team have regular communication with the pSITEs
    - Site initiation meetings; regular conference calls; newsletter; email blasts; training materials

- A Reliance Agreement is a written agreement between FWA-holding institutions, 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

- Content is generally consistent, but scope can vary

  - Programwide agreements with WCG IRB, Advarra, NCI CIRB

  - Master Agreement with SMART IRB

  - Regular NIH template for a single protocol

- Reliance Agreement is typically established *BEFORE* the participating site is added to a protocol

Principles

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
- When relying on an external IRB, the expectation is that the external IRB takes the lead deciding how to document the reliance arrangement

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

Process
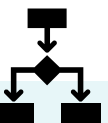
NIH is the Reviewing IRB: Creating a Participating Site shell in PROTECT

- A pSite is added to the protocol AFTER the Reliance Agreement is in place

- Only possible if the study has been identified as a **multi-site** in PROTECT as this switches *on* the PROTECT multi-site functions

- The Reliance Specialist creates the pSite in PROTECT and this provides a *shell* for the future submission of pSite documents to the NIH IRB

- Until then, pSite dashboard displays a status of *"Awaiting Study Materials"*

- The *creation* of the pSite in PROTECT is therefore **NOT equivalent** to an **IRB approval** of the pSite

NIH is the Reviewing IRB: Creating a Participating Site shell in PROTECT

NIH is the Reviewing IRB: Creating a Participating Site shell in PROTECT

- Creating the pSite shell in PROTECT needs the **pSite Institution** to have an *Institutional Profile* and the **pSite PI** having a PROTECT account - this involves:

  1. NIH study team submitting an account request to PROTECT Help Desk – this can include an Institutional Profile request

  2. pSite PI logs into PROTECT with credentials and completes PROTECT training

- NIH study teams can request an account at any time, but idea is at the time of the **Reliance Request**

NIH PROTECT Help Center

| NIH PROTECT Migration Information and FAQs | NIH PROTECT User Guides and TIP Sheets | How to get an Account for New PROTECT Users |

Get PROTECT Help/Support
Choose this form if you need assistance from a trainer with your work in PROTECT

PROTECT Issues
Choose this form if you are experiencing issues with various PROTECT components

Request Account in PROTECT (NIH user)
Choose this form if you are affiliated with NIH IC

Request Account in PROTECT (External Participating Site User)
Choose this form to request an account in PROTECT for the Participating Site (pSITE) PI or Study Coordinator at an institution that will be relying on the NIH IRB

4 ***Common pitfalls*** when trying to put a Reliance Agreement in place at the NIH

1. Reliance Request submitted prematurely

2. Reliance workflow at each Reviewing IRB and Participating Site differs

3. When NIH relies on an External IRB, a lack of awareness about the NIH institutional review

4. When NIH will be the Reviewing IRB, Participating Site study teams often unaware of their own sites' requirements

5. SMART IRB being viewed as an IRB and related confusion

Pitfalls

TIMELY not EARLY SUBMISSIONS

- Submit when the protocol is approved or very close to being approved (except if NIH is going to be the Lead Site and will be relying on an External IRB)
  - Approval means there is clarity about which 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
- Avoids duplication and redundancy – contributing to increased efficiency

MISALIGNED RELIANCE WORKFLOWS

- Find out the external IRB's submission 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

- Learn what NIH requires from the NIH study team planning to rely on external IRB
- Tell pSites to find out their own local processes and identify what they need from the NIH

Pitfalls

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 version 2 signatory
- Its use is documented on a study-by-study basis via SMART online platform or Letter
  - NIH study teams are advised by IRBO **if/ when** the online platform is needed
- 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.

Pitfalls

Adding a pSite to the Protocol

- Occurs after the Reliance Agreement has been executed and IRBO has created the pSITE shell in PROTECT

- pSites responsible for submitting their materials in PROTECT

  - NIH study teams no longer manages this process

    - NIH study team should have awareness about what the pSite is submitting and help facilitate when needed

  - pSite submissions usually reviewed via expedited review

- NIH IRB will review and approve:

  - pSite specific documents e.g., consents/assents
  - Recruitment materials that require revisions per the site or have unique text
  - pSite Protocol Addendum: Supplements the pSite Application in PROTECT; provides important local context information about the institution and how the protocol will be implemented there

- pSite HRPP Clearance is also required per NIH HRPP policy 105. Documents confirmation that pSite's institutional requirements are met and local context information provided is vetted by the relying institution
  - Documented via a letter, email, memo, etc. (no set template)

- NIH IRB only approves the pSite Principal Investigator. Expectation is that the pSite will review pSite study team members per its institutional requirement

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Potential Pitfalls when adding a pSite to the Protocol

- IRB unable to fully assess local context at a pSite
  - pSite does not submit the pSite Protocol Addendum (or it is not fully completed)
  - pSite does not correctly complete its documents based off the model versions
    - Does not include required language
    - Does not follow prompts to complete site-specific language
    - Adds language that is not acceptable
    - Does not provide documentation of policy requirements for certain revisions to the ICF

- Lead and/or pSite have not factored in the time/effort in securing ancillary reviews at the site

- QA check no longer exists now that the NIH team does not submit for pSites in PROTECT
  - Suggest good and robust communication between the Lead site and pSites

- HIPAA Privacy Rule expectations: NIH is not a covered entity. NIH IRB does not serve as a Privacy Board. Participating Sites that are covered or hybrid entities need to manage how they will adhere to HIPAA Privacy Rule requirements by working with their Privacy Boards.

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

NIH Study Team:

- Submits **Study-Wide** Modifications, Continuing Reviews*, Event Reports (both NIH site reportable events and pSite reportable events), and Study-Wide Closures

- Ensures protocol compliance and safety monitoring

- Facilitate audits

- Serves as the key communicator between the Reviewing IRB and Participating Sites

pSites:

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

*NOTE: pSites are responsible for reporting CR data in PROTECT to the NIH study team. The NIH Study Team is responsible for creating and submitting a CR that encompasses the entire multi-site study.
See **PROTECT: NIH is the Single IRB of Record Guide** for more information.

NIH and Site-specific Reportable Events

- The NIH PI, as part of the Lead Site, is responsible for ensuring that all reportable events are communicated to the 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 IRB
    - Communication between the NIH PI/Study Team and pSite PIs/Study Teams is important to guarantee reportable events are submitted efficiently and accurately

- Reportable New Information (RNI) forms can be submitted by anyone who has an active user account in the PROTECT system

- 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*
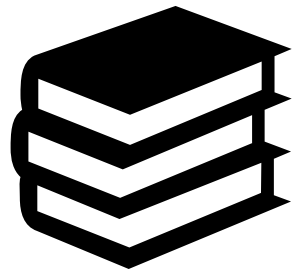
- **Modifications**:
  - NIH study team not promptly notifying all sites of study-wide amendment approvals
  - Not factoring in the time it can take to approve a study-wide amendment, then the subsequent pSite amendments e.g., model ICFs, then pSite ICFs
    - Communicate with pSites when study-wide amendments will require pSites to modify their documents
      - This can affect reconsenting timeframes, as well as consenting new subjects

- **Continuing Reviews:**
  - With the CR process in PROTECT, communication between the NIH study team and pSites is key to get accurate/timely data submitted prior to the NIH study team submitting the CR

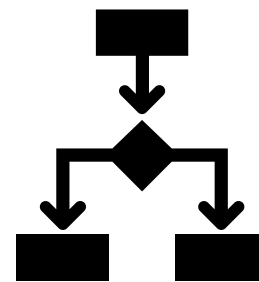# *Potential Pitfalls* when Maintaining a Multi-site Study - RNIs

- **Reportable Events/ Reportable New Information:**
  - As with CRs, communication is key so the NIH PI/Study Team is aware of reportable events being submitted by pSites and vice versa.
    - The pSite PI submits an RNI directly to the IRB in PROTECT. PROTECT does not send notification to the NIH PI when this happens. The pSITE PI needs to also notify the NIH PI when an event occurs and is reported to the IRB.
      - The NIH PI can view the RNI in PROTECT (the NIH PI cannot edit or process the RNI)

  - pSites need to be aware of possible dual reporting requirements. Many, if not most, institutions require that sites ceding IRB review still report certain events to its institution (usually its IRB)

PART 2:

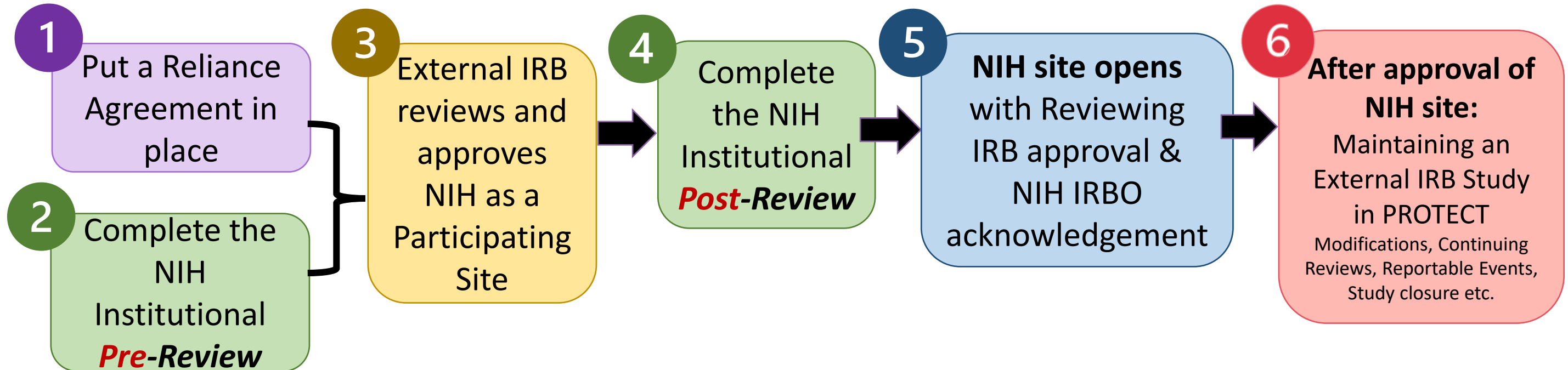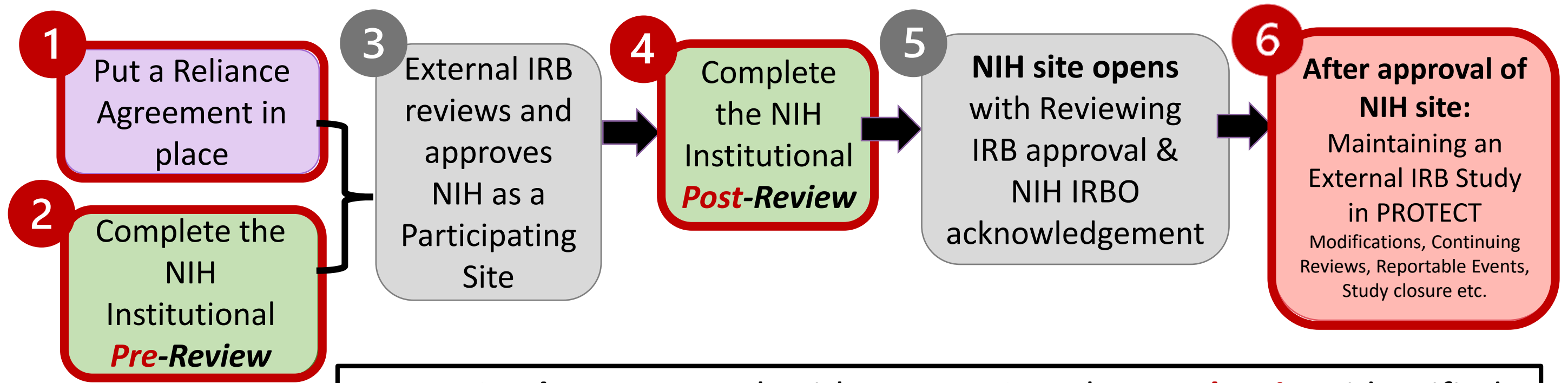## Adding NIH as a site on a protocol that is being reviewed by an external Reviewing IRB

Principles

Processes

Pitfalls

Overview: Process of NIH Relying on an External Reviewing IRB

1 Put a Reliance Agreement in place

2 Complete the NIH Institutional *Pre-Review*

3 External IRB reviews and approves NIH as a Participating Site

4 Complete the NIH Institutional *Post-Review*

5 **NIH site opens** with Reviewing IRB approval & NIH IRBO acknowledgement

6 **After approval of NIH site:** Maintaining an External IRB Study in PROTECT Modifications, Continuing Reviews, Reportable Events, Study closure etc.

- This diagram illustrates the steps **NIH teams** should follow when they want NIH involved in a study reviewed by an External Reviewing IRB

- Documents the workflow for NIH to:
  (i) Rely on an **External Reviewing IRB** and
  (ii) Added as a **Participating Site (pSite)** on the external protocol

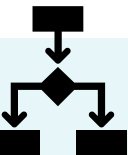NIH Office of Intramural Research
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6 After approval of NIH site: Maintaining an External IRB Study in PROTECT Modifications, Continuing Reviews, Reportable Events, Study closure etc.

- **NIH Study Teams** work with **NIH IRBO** at the **touchpoints** identified
- The objective at each **touchpoint** is to provide the Reviewing IRB the information it needs to be able to provide appropriate IRB oversight of the NIH's research activities and/or ensure that the NIH operates in compliance with our own FWA and local policies
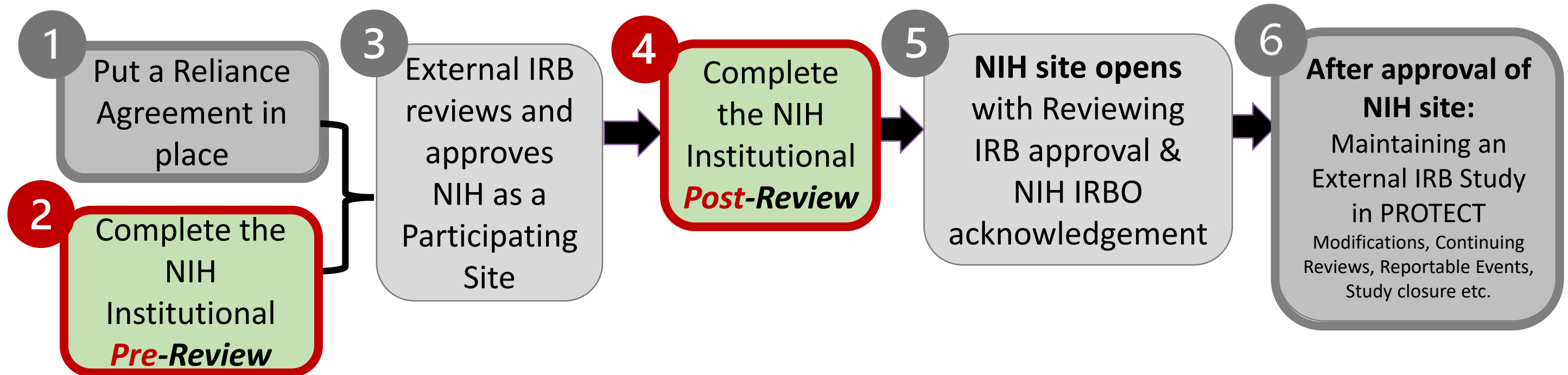
Process

Process of NIH Relying on an External Reviewing IRB – **Touchpoints** with IRBO

Putting a Reliance Agreement in place

Completing the NIH Institutional Review Process
(**pre**- and **post**)

After approval of NIH site:
Maintaining an External IRB Study in PROTECT

Overview: Process of NIH Relying on an External Reviewing IRB

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6 After approval of NIH site: Maintaining an External IRB Study in PROTECT
Modifications, Continuing Reviews, Reportable Events, Study closure etc.

The *principles* behind the NIH Institutional Review Process

- NIH <u>only</u> *cedes* IRB review to an external IRB to review and approve NIH's research activities
- NIH **retains responsibilities** and ensures compliance with NIH requirements through:
  - **①** **IRBO Administrative Reviews:** Ensure the conduct of the research and the content of NIH site documents complies with NIH requirements at the outset and on an on-going basis
    - Before 1st submission to the External IRB, it involves a Pre-Review & Post-Review
      - **Pre-Review:** Provides NIH teams clearance to submit to the External IRB for the first time
      - **Post-Review:** Acknowledges External IRB approval of the NIH and allows study to open
    - After NIH is approved as a site, admin reviews take place after the External IRB review
  - **②** **External IRB Study in PROTECT:** The submission in PROTECT facilitates IRBO's admin reviews and allows it to track all external IRB approvals and study documents (including the IRB-approved protocol and NIH consents) for the duration of the study
- External IRB **approves** the NIH site, NIH IRBO *acknowledges* the external IRB approval

The *process* behind the NIH Institutional **Pre-Review**

- Clearance to open a new study at the NIH is completed in 2 stages: a **pre-review** and a **post-review**
- NIH Study Team needs to create and submit a new study in PROTECT that identifies that an external IRB will be used – this is known as an **External IRB Study**
- Creates a shadow protocol to mirror what is submitted to the external IRB and facilitates the completion of applicable ancillary reviews
- The pre-review submission can happen in parallel to, or after, the reliance has been documented

PRE-REVIEW
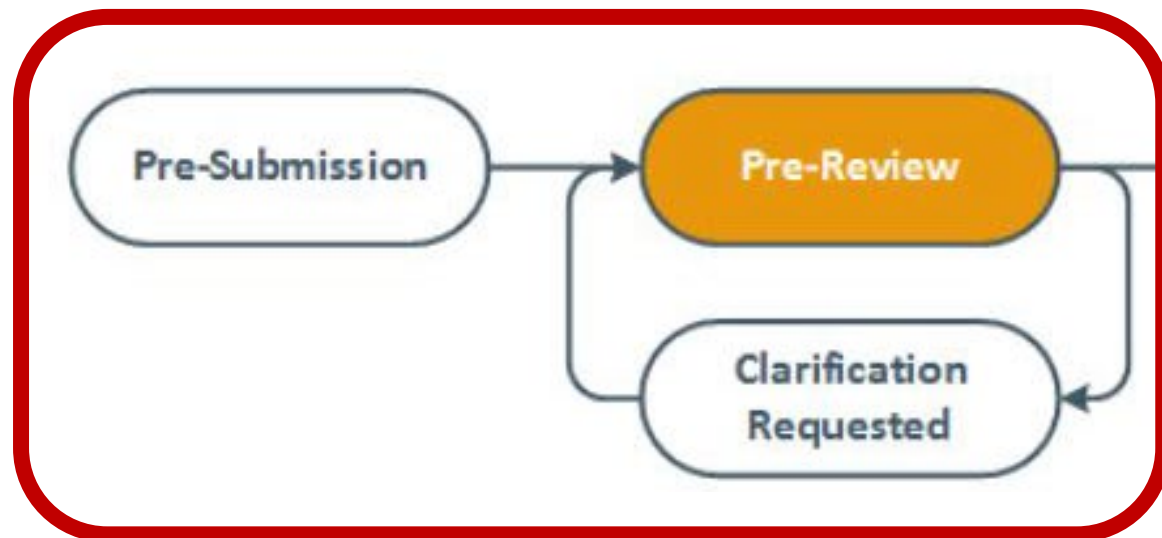
POST-REVIEW

Process
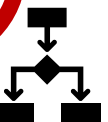
The **Pre**-Review *process*

① Pre-Submission

NIH Team *provides:*

- Sponsor Protocol ☑
- NIH Protocol Addendum ☑
- Model Consents/Assents ☑
- NIH Consents/ Assents ☑
- Recruitment Materials ☑
- Investigator Brochure/ Package Insert ☑
- Applicable Ancillary Reviews ☑
- HRPP Training ☑

② Pre-Review

NIH IRBO *reviews to:*

- Ensure NIH Protocol Addendum meet NIH requirements
- Confirm NIH required language in consent/ assent documents
- Verify completion of Ancillary Reviews
- Check HRPP Training Records
- Provide Institutional Local Context

③ Clarification Requested

- **IRBO** issues NIH Institutional Review Memo
  - Confirms submission meets NIH requirements
- **NIH Study Team** can submit to Reviewing IRB
 - Provides memo to Reviewing IRB

The Post-Review *process – Activation of the NIH site*

- After NIH site is approved by the External IRB, the NIH Study Team submits a "Response to Clarification Requested" and updates PROTECT with external IRB letter(s) and approved documents

- IRBO reviews documents to ensure remain consistent with NIH institutional requirements

- Captures pertinent information e.g., risk determination for a specific population & expiration date

- Issues an **Acknowledgement Letter** noting NIH is approved as a site

- NIH site is Activated when "Review Complete"

- If at the NIH Clinical Center, documents move forward to Office of Protocol Services for processing
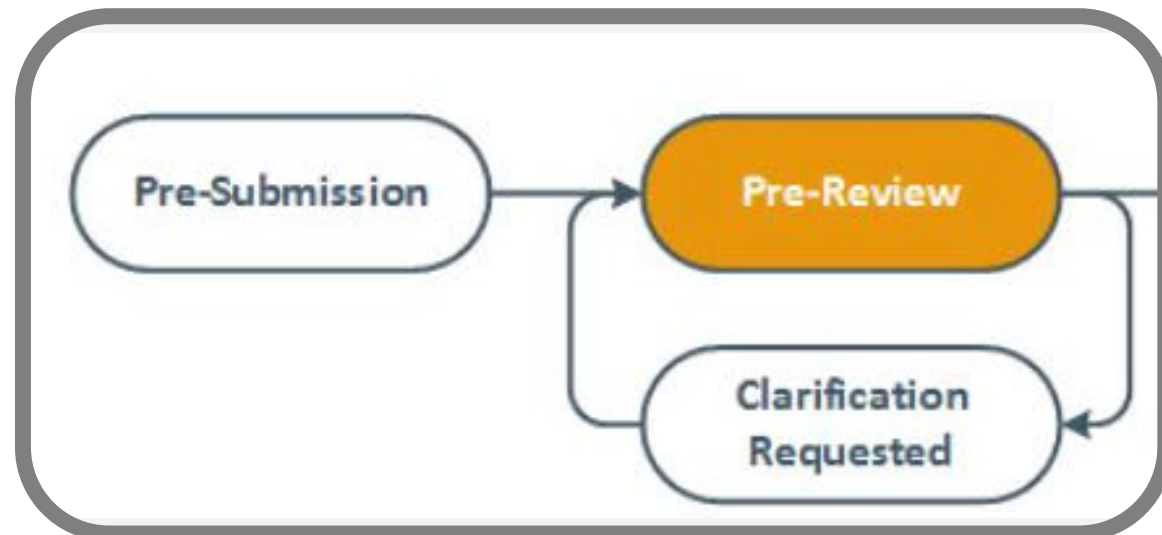
PRE-REVIEW **POST-REVIEW**
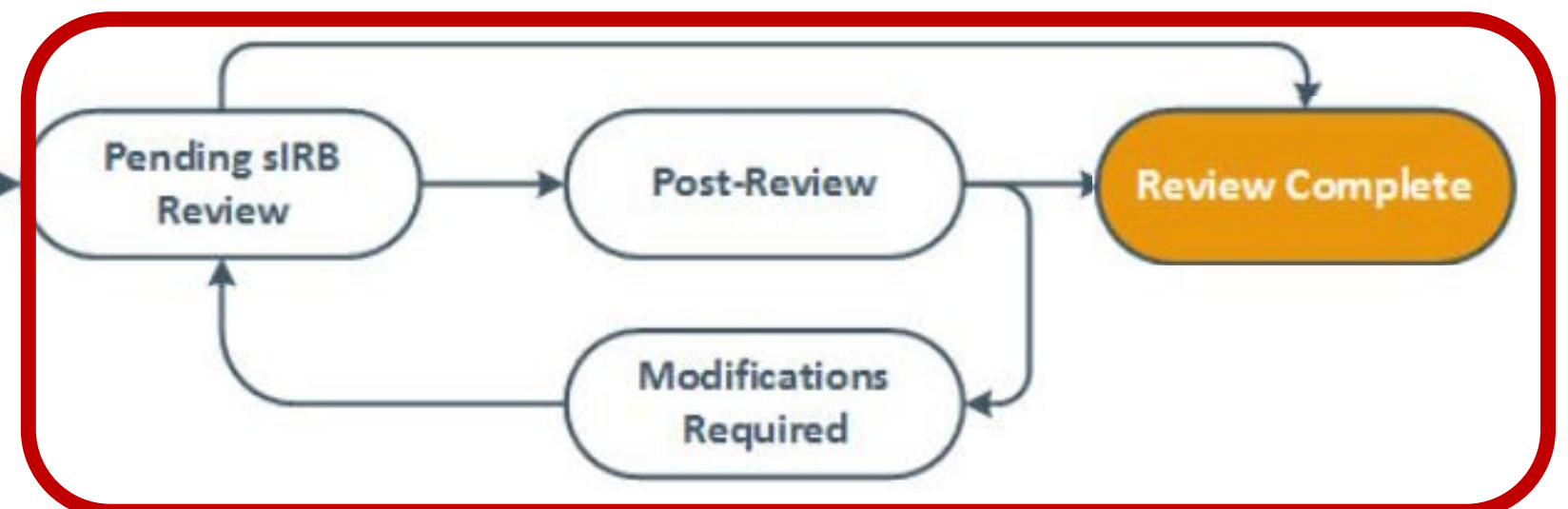
The *potential pitfalls* of the NIH Institutional Review Process

1. Lack of clarity about the External IRBs processes vs NIH's requirements

2. Involvement of third parties in the External IRB submission process

3. Lack of detail in External IRB letters

4. Preparation of NIH Protocol Addendum and NIH Site Consents

5. Recognizing that NIH is not the Reviewing IRB but has a vested interest

Pitfalls

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Tips to avoid the *pitfalls*

#1. *LACK OF CLARITY*

- Find out the external IRB's submission process and identify any conflicts
  - Do they tie reliance execution with review of NIH site?
  - Are they using an additional online platform e.g., iREX?
  - Do they require 2 part-consents vs standalone NIH site consent?

#2. *EXTERNAL IRB SUBMISSION PROCESS*

- Establish whether NIH team submits directly to the External IRB
- If not, ensure that 3rd parties' loop in the NIH team

#3. *EXTERNAL IRB LETTERS*

- Keep in mind IRBO's goal – ensuring NIH has IRB approval for its research activities
  - IRB determinations (risk, vulnerable populations, consent waiver, expiration etc.)
  - Study-wide documents and NIH documents have been reviewed and approved

#4. Tips for preparing the *NIH Protocol Addendum*

- Describe NIH's role in the research and identify relevant institutional requirements

- Ensure that Reviewing IRB understands protocol implementation at the NIH

- Intention to supplement Main Protocol and to be read in conjunction with it

  - Correct statements that something will be done at the NIH site when it won't

  and/or

  - Describe when NIH will do something *differently/ in addition* to the protocol

- Avoid defaulting to language that is submitted when NIH is the reviewing IRB

- Should not duplicate the protocol

#5. Tips for preparing the *NIH Consents/ Assents*

- Find out how the Reviewing IRB wants to review Site Consents – 2 part/ single

  - Typical approach is for NIH required language to go into Model Consent
  - <u>Do not</u> start the process using the NIH template as the base document

- Establish if the protocol is being reviewed under the Revised Common Rule, if so, ensure compliance e.g., develop a Key Information section etc.

- Content needs to be consistent with the NIH Protocol Addendum

- Acceptable to retain language from the Model when equivalent to NIH template language, with exceptions e.g., research-related injury

- Evolving craft and NIH is flexible as external IRBs take different approaches

- Contact IRBO for consent guidelines if additional assistance needed

Tips to avoid the *pitfalls* – Examples of typical consent customizations

RESEARCH PARTICIPANT CONSENT ~~AND PRIVACY AUTHORIZATION FORM~~

Study Title: Multi-Site Research on Long Covid

~~Site~~ Principal Investigator (Study Doctor): [NIH PI's Name] ~~Lead Investigator at external site~~

~~NIH~~ IRB#:   [PROTECT #]~~17-007708~~

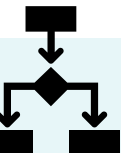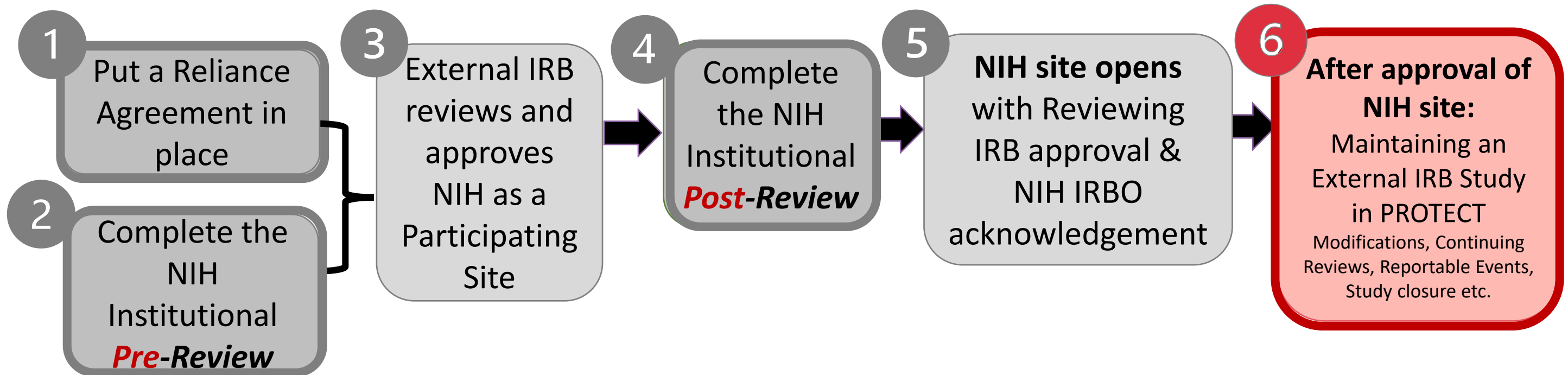~~Study Site:~~   National Institutes of Health [include address if model consent requires it]

Additions:

- NIH IRB number
- NIH CC header and footer
- Compensation & reimbursement text
- NIH research-related injury language
- Certificate of Confidentiality and Privacy Act
- Appropriate sections of NIH signature block
- Key Information section and revised Common Rule elements

Deletions:

- HIPAA-related text
- Assertions that insurance will be billed
- Assertions that subjects can continue clinical care at the NIH if withdraw from study
- References that combine Sponsor and Study Site conduct or responsibilities

Overview: Process of NIH Relying on an External Reviewing IRB

1 Put a Reliance Agreement in place

2 Complete the NIH Institutional **Pre-Review**

3 External IRB reviews and approves NIH as a Participating Site

4 Complete the NIH Institutional **Post-Review**

5 NIH site opens with Reviewing IRB approval & NIH IRBO acknowledgement

6 After approval of NIH site: Maintaining an External IRB Study in PROTECT
Modifications, Continuing Reviews, Reportable Events, Study closure etc.

Process of NIH Relying on an External Reviewing IRB – Touchpoints with IRBO

Putting a Reliance Agreement in place

Completing the NIH Institutional Review Process (**pre-** and **post**)

After approval of NIH site: Maintaining an External IRB Study in PROTECT

The *principles* behind maintaining an External IRB Study in PROTECT

- NIH retains responsibilities when it *cedes* IRB review to an external IRB
- NIH requires study teams to maintain an External IRB Study in PROTECT
- For the duration of the study, it allows NIH IRBO to:
    - Confirm on-going IRB approval of NIH's research activities
    - House approved versions of key study documents (e.g., protocol, NIH consents)
    - Conduct admin reviews of study actions e.g., modifications, continuing reviews
    - Review NIH study team changes
- Assists teams to comply with ancillary review requirements e.g., DEC review
- Close study when NIH's research activities have ended

- Maintaining an External IRB Study assists teams comply with requirements in [NIH HRPP Policy 105](#), which outline that NIH PIs are expected to:
  - Comply with applicable Reviewing IRB and NIH policies
  - Inform IRBO when:
    - The study has closed (either the overall study or at the NIH site);
    - There is a change in the NIH PI; or
    - There are any changes to the research that might impact any terms of the reliance agreement
  - Submit to IRBO upon receipt all external IRB approvals, including the IRB-approved protocol and consents

The *process* behind maintaining an External IRB Study in PROTECT

SUMMARY TABLE: Study Update vs Site Modification for Multi-Site External IRB Studies

		SITE MODIFICATION
Important Reminder:	If there is a change to **both** the protocol and NIH local site documents, you will need to create **two** submissions to properly document the change, a *Study Update* and *Site Modification*.	
	STUDY UPDATE	
When to Use:	To document changes to study-level documents, the NIH addendum, CRs and NIH closing as a site.	To document changes to NIH site documents (except NIH addendum) and NIH study team (if NIH PI change, must select scope as "Other parts of the site")
How to submit:	There is no "Submit" button. Instead "Add...	Click "Submit" No need to "Add...

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PROTECT

External IRB Guide

Once the NIH site is approved, the IRBO admin review process does not have a pre and post review component. Teams submit to IRBO **AFTER** the External IRB has approved an action

Teams must include an **External IRB Letter** with each submission (except non-PI personnel changes) so that NIH IRBO can verify changes are approved

EXTERNAL IRB PROTECT GUIDE:
https://irbo.nih.gov/confluence/display/ohsrp/NIH+PROTECT+User+Guides+and+TIP+Sheets

The *process* behind maintaining an External IRB Study in PROTECT
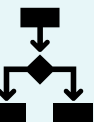

External IRB functions depend on whether study is single or multi-site (MS)

If MS, change are submitted either as a **Site Modification** or **Study Update**

Continuing Reviews come in as **Study Updates** not "Reporting CR Data"

EXTERNAL IRB PROTECT GUIDE:
https://irbo.nih.gov/confluence/display/ohsrp/NIH+PROTECT+User+Guides+and+TIP+Sheets

Potential pitfalls behind maintaining an External IRB Study in PROTECT

1. Continuing Review (CR) Submissions
   i. Not using **Study Update** form
   ii. Late
   iii. Not coordinated well with DEC
2. Providing inadequate information in the summary of changes
3. Not including External IRB Letters
4. Assuming related actions will be reviewed by the same analyst
5. Not submitting actions into PROTECT in a timely manner

Pitfalls

Tips to avoid the *pitfalls*

#1 CONTINUING REVIEWS

- Review the PROTECT External IRB Guide to find out the CR submission process

- If covered protocol, initiate the Study Update early to allow time for the DEC review. The External IRB letter can be uploaded later, closer to the expiration date

#2 CONTENT OF SUBMISSIONS

- Be mindful of the intended audience (now and in the future)

  - Provide adequate information about the submission to facilitate the review

  - Avoid cross-referring to a parallel submission for information/ documents

  - If something is needed in **this** submission, include it in **this** submission

  - Submissions are not reviewed by just one analyst so cannot rely on their familiarity of the study

Tips to avoid the *pitfalls*

#3 EXTERNAL IRB LETTERS
- Don't forget to include them in the submission
- Carefully review the letters – do they list the approved documents? Are the documents listed consistent with what has been uploaded into PROTECT?
- If they don't list documents, provide other supporting documentation and an explanation

#4 ASSIGNMENT OF CEDED SUBMISSIONS
- Submissions are typically processed by the IRBO sIRB team not by a single analyst
- Related submissions will not necessarily have the same reviewer or processing time
- Ensure each submission includes all the documents needed for that specific submission
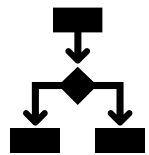
#5 UNTIMELY SUBMISSIONS
- Submit actions to PROTECT shortly after they've been reviewed by the External IRB
- Facilitates managing versions in PROTECT and avoids processing delays
- Protects against being non-compliant with NIH HRPP Policy 105

Learning Objectives

Principles

Provide a refresher on Single Institutional Review Board (sIRB) review principles ✅

Processes

Describe current processes for NIH study teams when:

- NIH is the Reviewing IRB
- NIH is relying on an External IRB

✅

Pitfalls

Discuss best practices for avoiding common pitfalls when working with an sIRB ✅

Contact Us

NIH IRB Reliance & sIRB Team

For further guidance or questions:

Web: [Reliance and sIRB IRBO webpage](#)
[Multi-Site Research (nih.gov)](#)

Email: [NIH-Reliance-sIRB@nih.gov](#)