Yale *Human Research Protection Program*

Continuing Reviews and Modifications

02.24.2025

Jennnifer Reese **Marta Boeke**

Yale *Human Research Protection Program*

Learning Objectives

- Learning Objective #1
  - Review IRES IRB system requirements for submission of modifications, Continuing Reviews, and Closures
- Learning Objective #2
  - Discuss the IRB review of the submissions to determine approvability
- Learning Objective #3
  - Offer best practices to ensure seamless review process

Training Agenda

Agenda Item	Slide #s
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General Comments

- The presentation will reflect Yale IRB review – studies under external IRB purview must follow policies and procedures of the reviewing IRB;
- The discussion will focus on non-exempt research (research that was approved by the IRB via expedited or convened board review procedures);
- Only the Principal Investigator or assigned PI Proxy can submit actions in IRES IRB system;

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Modifications

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IRB review of modifications

- Changes to approved protocols must receive IRB approval before their implementation
  - Exception: changes to eliminate an apparent immediate hazard to participants e.g., immediately stopping study treatment in a participant experiencing a serious side effect; must be promptly reported to the IRB via a Report of New Information.
- The IRB reviews proposed changes to determine whether the revised protocol continues to meet approval criteria and other regulatory and local requirements for human subjects research e.g., state statues, local policies, etc.
- Review of changes can be conducted via full board or expedited review procedures – level of review does not affect submission requirements

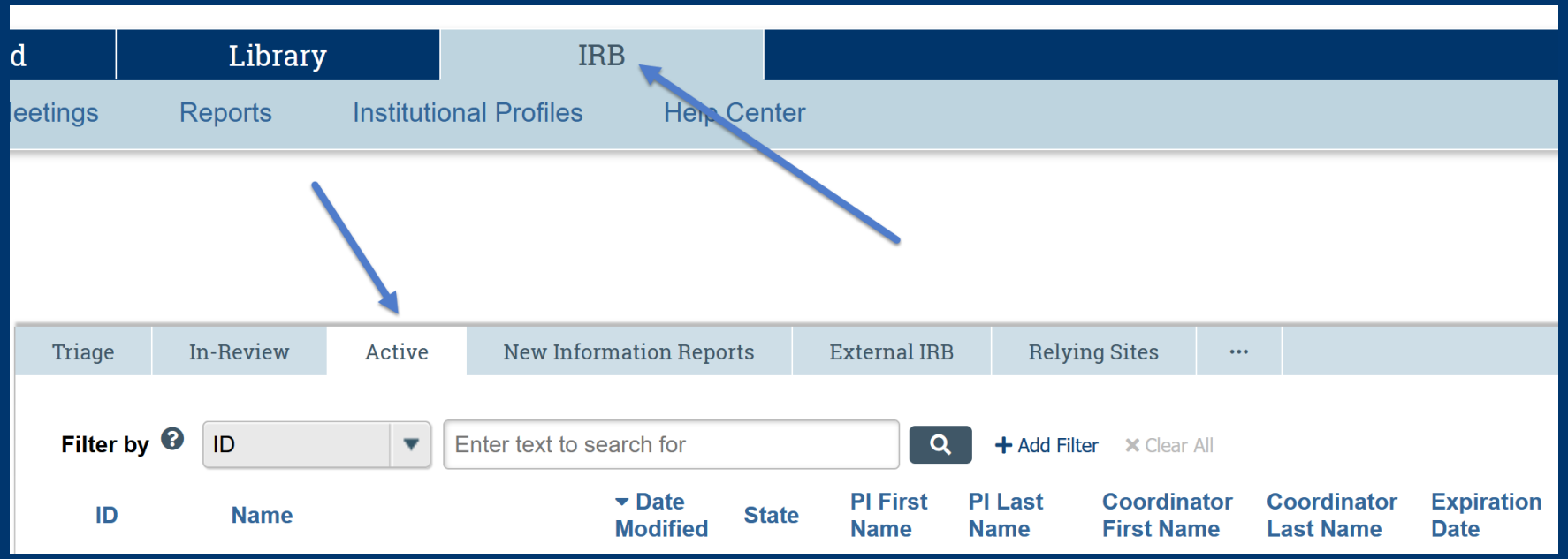
Study Modifications

Changes in research include, but are not limited to:

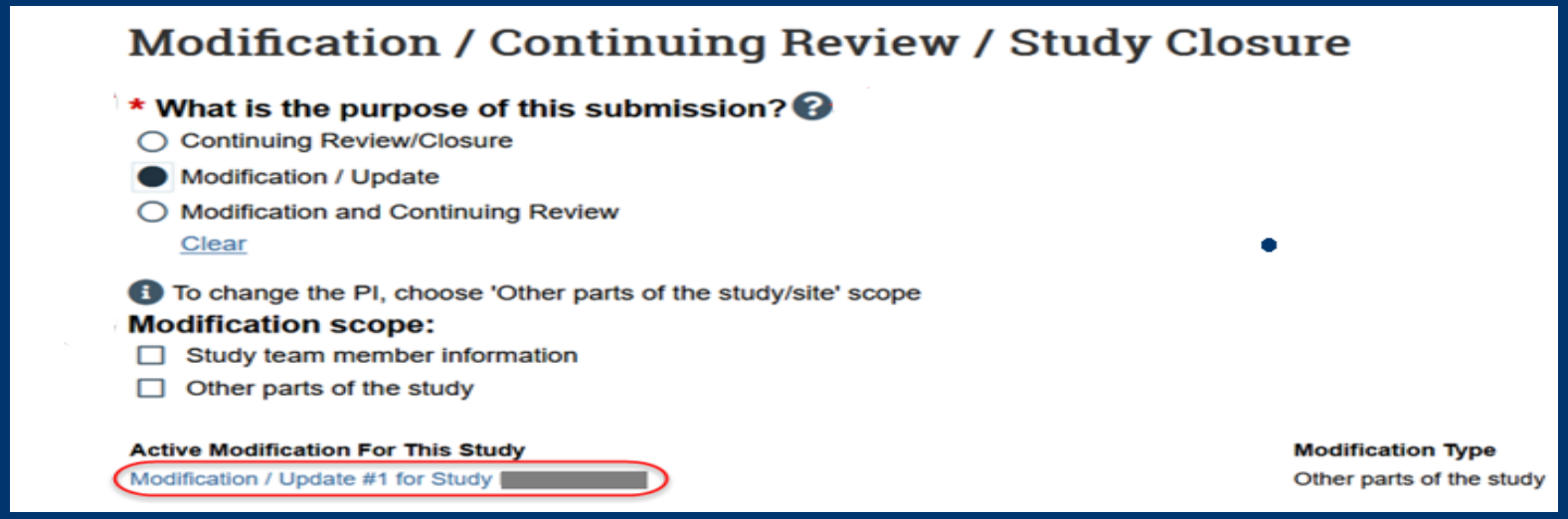
- Modifying or adding research documents, including the study protocol, consent form(s), investigator's brochure, surveys, or other study documentation;
- Changes in research locations, which require revision to the pages in IRES IRB;
- New risk information regarding the study drug or device, described in the informed consent form(s);
- Addition of a study drug/device;
- Addition of a new research procedure not already approved by the IRB;
- Change in funding;
- Change in targeted enrollment, addition of a vulnerable population, or change in duration of the study;
- Change of PI or investigators;
- Change in the financial or personal interest of the PI or the study personnel (investigators or assistants).

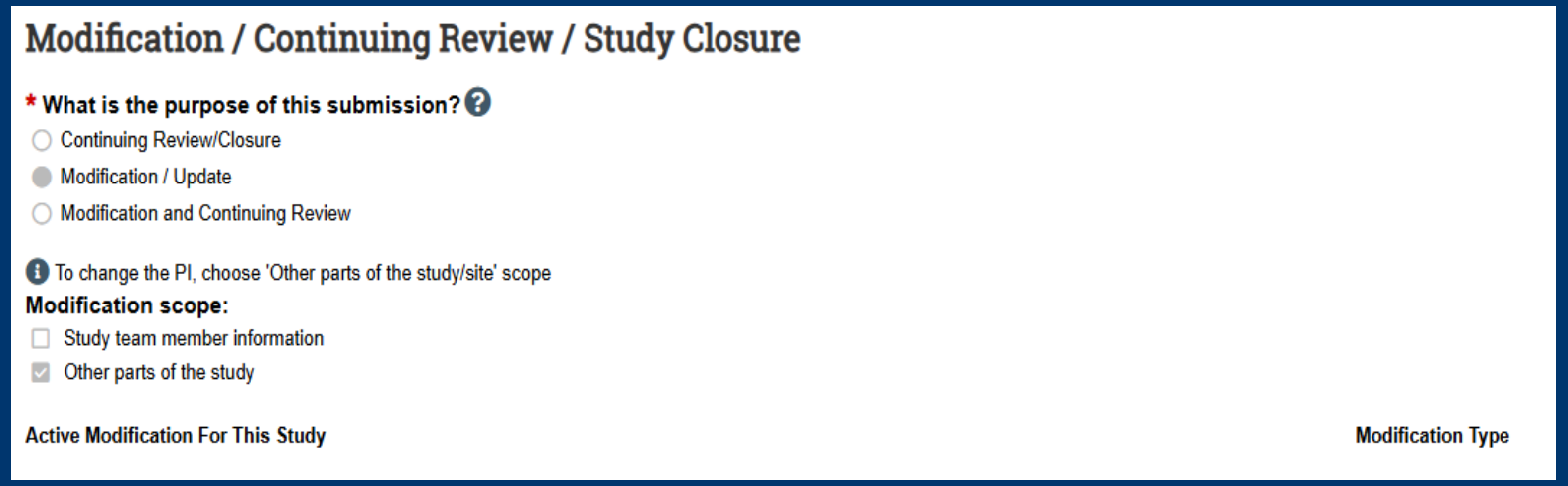
Steps in IRES-IRB platform for MOD submission

- Locate approved research project in Active tab, IRB section of IRES IRB
- Click on Create Modification/CR in the study workspace



Submission of a MOD

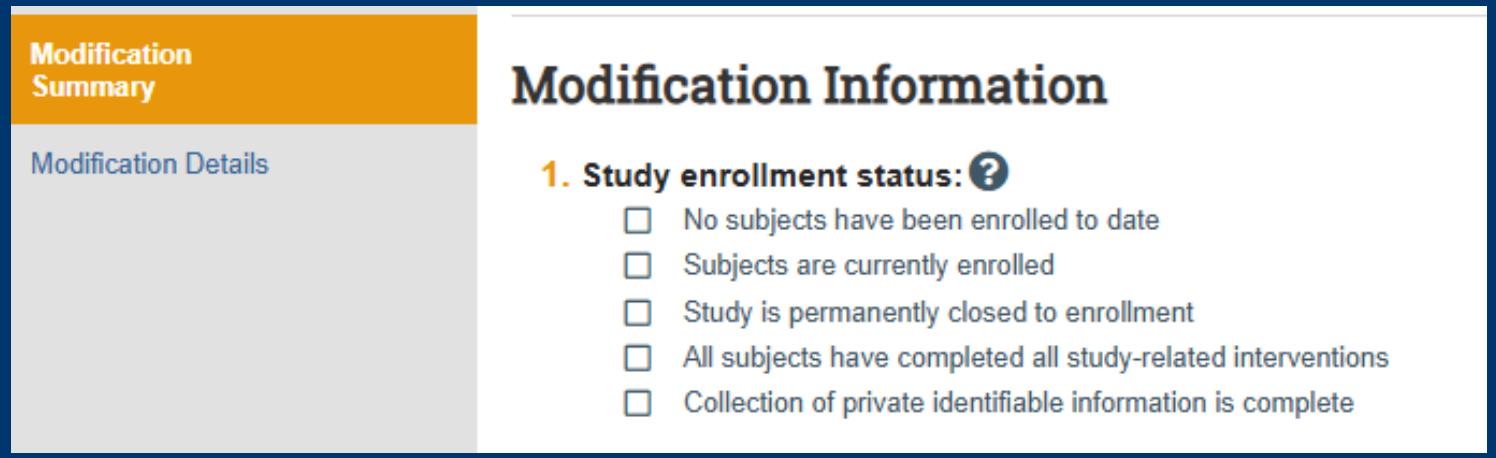




- After you select the submission purpose and continue to the next form, you cannot change the submission purpose or scope.
- It's best practice to submit personnel changes separately from other types of modification - they are faster to review.

Study Modifications cont.

When submitting modifications for IRB review, you need to provide the study enrollment status to determine if the changes are applicable to the Yale site. Choose all applicable options from the list in Question 1.

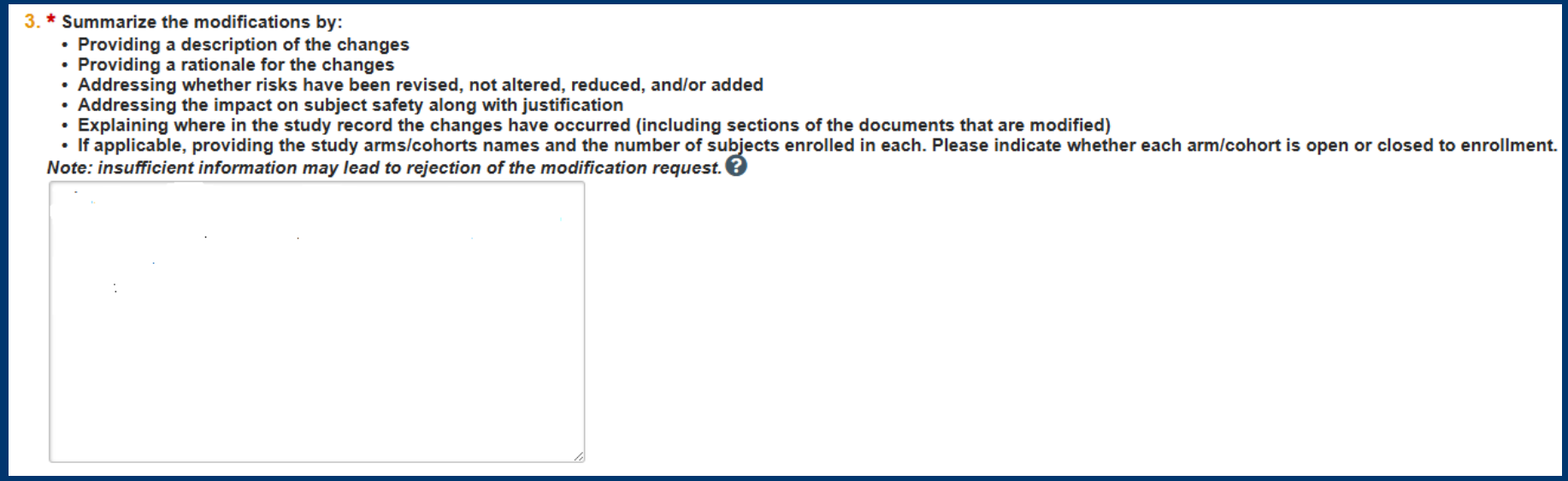


Note: "All subjects have completed all study-related interventions" AND "Collection of private identifiable information" should only be checked if the study is also permanently closed to enrollment.

Study Modifications cont.

When submitting modifications for IRB review:

- Provide a summary and rationale for the changes;
- Address how the change affects the risks and subject safety;
- Explain where in the study record the changes have occurred (including sections of the documents that are modified);
- If changes affect only certain cohorts, provide the names of the study arms/cohorts and indicate their status e.g., closed to enrollment, etc.


3. * Summarize the modifications by:
- Providing a description of the changes
- Providing a rationale for the changes
- Addressing whether risks have been revised, not altered, reduced, and/or added
- Addressing the impact on subject safety along with justification
- Explaining where in the study record the changes have occurred (including sections of the documents that are modified)
- If applicable, providing the study arms/cohorts names and the number of subjects enrolled in each. Please indicate whether each arm/cohort is open or closed to enrollment.

Note: insufficient information may lead to rejection of the modification request.

Suggested Language

1. We are submitting the following modification...
   - The sponsor has revised the protocol as follows: for example, inclusion of individuals 5-17 years old.
   - A new version of the IB is available with the following changes: risk of blood clots, increased risk of heart attack from 1 to 10%
   - We want to revise the aims of the study as follows:
   - We are adding two new enrolling sites

2. The change is needed because … (*rationale for the changes*)

- New safety data is available
- We want to explore a new population
- We received new funding for this purpose
- Our experience/ current literature/standards are as follows and we would like to revise the study to be consistent.

Suggested Language cont.

3. The following documents are *revised/added*: X, Y, Z

<u>Note</u>: Remember to include sponsor consent templates, tracked protocols, and/or tracked IB's where applicable

4. A summary of the changes can be found: …

- In the new Sponsors protocol page:
- In the tracked IB page:
- In the Sponsor memo

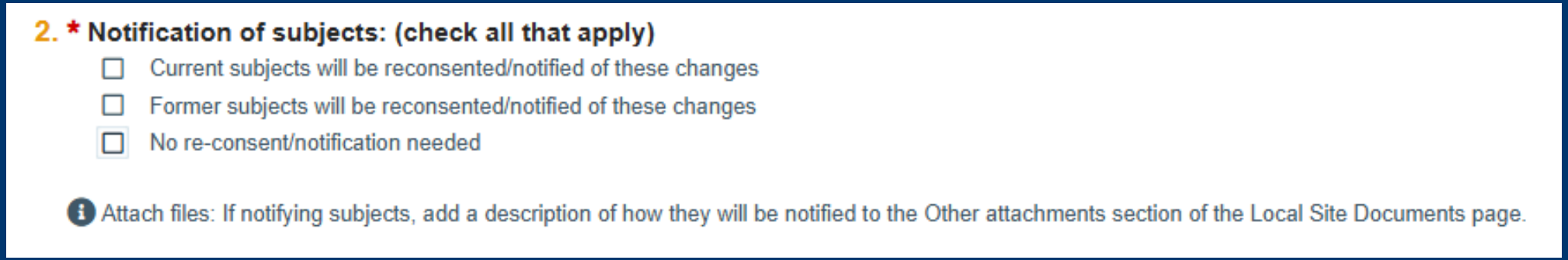
5. Risks to subjects are revised/not altered/reduced/added. The consent forms have/have not been revised.

6. We do/don't believe this impacts the safety of participants of the research …because…(justification of the safety)

7. Subjects will be notified about the new information. This is our plan for notifying the participants:….

Notification of participants (question #2)

- Certain changes may require notifications to participants;
- Regulations do not include a term '***reconsent***' but they require that participants are notified about any significant new information that could impact their willingness to continue in the study;
- Think about whether the new information is significant, and if so, who could be impacted by it – answer question #2 and provide a more detailed plan in question #3



Consideration for determining whether to re-consent

Questions	Considerations
Who must be notified or have consent re-obtained? • All subjects ever enrolled in the study regardless of their current status • Only subjects active on study intervention or another subset of subjects	Does the change affect different groups of subjects differently? If so, which groups of subjects are affected? Does it depend on the subject's status (active, previously enrolled), arm of the study, or gender or age groups? Will the impact of the change affect subjects after the study is complete?
What exactly is the change that requires communication? • New risks • New inconveniences • New procedures • New treatment alternatives • New costs • Other significant findings	Could the information affect a subject's willingness to continue participation? Will the change require a different level of commitment from the subject; e.g., additional procedures?

Reconsent requirements based on study status: Active Participants

Active Study Participants	
New Information Likely to Affect Participants	**Information Not Likely to Affect Participants**
• New or increased risks of the study intervention/study procedures • Additional study procedures required by the study; e.g., additional Lumbar Puncture or MRI • Changes in doses or frequency of the study drug • Modifications to the study design; e.g., timeline of their study visits • Changes to payments or cost for participation; e.g., previously provided drug now being charged to participant's insurance, changes to remuneration • New FDA approval of drugs involved in the study or those that create new alternative treatment	• Administrative changes such as the date or version number of the consent form • Modifications to the arm of the study that does not apply to all participants; e.g., changes for non-smokers while the subject is enrolled in the arm for smokers • Addition of procedures that the subject will not be asked to undergo; e.g., baseline MRI • Minor editorial changes in the consent/protocol for clarity

Reconsent requirements based on study status: follow up or off study

Previously Enrolled Study Participants Who Concluded Their Participation	
Information Likely to Affect Participants	**Information Not Likely to Affect Participants**
• Newly discovered long term side effects of the study drug • New adverse events associated with the implanted study device	• New short term side effects of the study drug/procedure • Changes to the study design • Any information that would not affect currently enrolled subjects

Study Modifications – Best Practices

- Ensure that the proposed revision is reflected in all applicable documents and the IRES IRB record. For example, information about payments for participation needs to be consistent in the protocol/ICF/IRB Submission Form, recruitment flyers, and other recruitment documents.
- Ensure the PI approves the final revisions prior to IRB submission.
- Revisions to documents must be tracked using 'track changes' function – do not upload clean versions.
  - Highlights or using a different color font will not be accepted.
  - Maintain electronic copies of all information submitted to the IRB in case revisions are required.

Best Practices cont.

- Download WORD version of the approved documents from DRAFT column in Documents tab in the Study Workspace. Accept previous changes but don't stop tracking new changes. Make the proposed changes into the document and save it as a new version.

- Follow a reliable method of version control of your documents – use whatever method works for you as long as it is consistent.

Uploading documents:

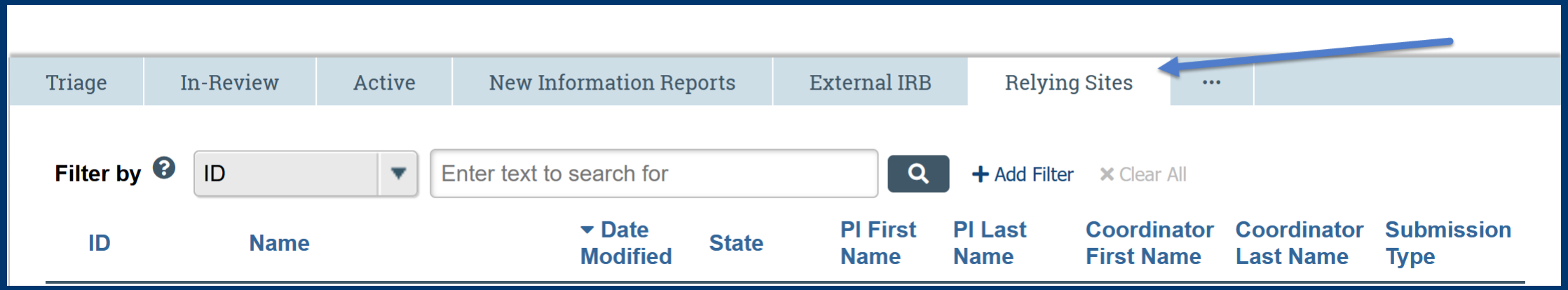
- Choose "Update" to upload tracked versions of previously approved documents
- Choose "Add" if the document is new and there are no previous versions of this document in the study record.
- !!! Do Not delete any study documents!!!

IRB review outcomes

Decision	Meaning	Approved Documents
Approved	Modification does not change the approval criteria; if participants must be notified about the changes, directive will be included in the approval letter;	Approval watermarks are applied to Consent documents and Protocol if they have been revised
Modifications Required	Modification does not affect the approval criteria and there are only minor revisions must be made, the revisions cannot be implemented until a response to the required modifications is submitted and approved;	No approval watermarks will be applied until a final IRB approval is issued
Deferred	Modification does affect the approval criteria OR there is no sufficient information to determine whether the approval criteria are affected – the investigator is asked to address specific approval criteria; a response must be reviewed at a convened board before a new determination is made;	No approval watermarks will be applied until a final IRB approval is issued
Disapproved	Modification affects the approval criteria in a way that study is no longer approvable; the investigator must submit a new modification for review;	No watermarks are applied

Modifications to multi-site research where Yale serves as the single IRB

- Submit the modification to the protocol and Yale documents first;
- Once approved, submit modification to the site specific documents by creating a Site Modification from the site workspace - identify the site in the ***Relying Sites*** tab



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Continuing Reviews

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Continuing Review Requirements

- Minimal risk studies not subject to FDA or DOJ oversight - approval can be granted without the requirement for continuing review. For minimal risk studies, the IRB reserves the right to request an annual review with a rationale for doing so.

- Greater than minimal risk studies or studies subject to FDA or DOJ oversight - the IRB will conduct continuing review of research at intervals appropriate to the degree of risk of the research, but not less than once per year;

Expiration Dates

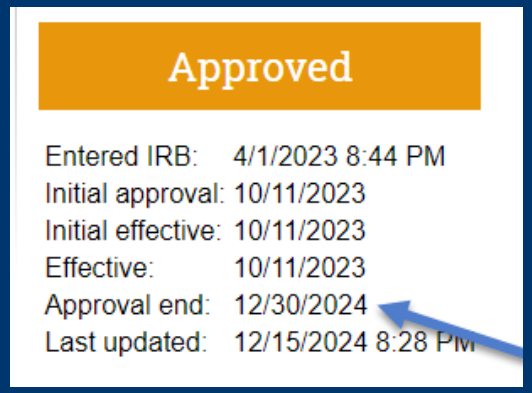
- The expiration date is based on the most recent approval of the study – either initial approval or the most recent continuing review;

- Each year's expiration date may be different – Yale IRB does not maintain the same anniversary date of the approval;

- As a courtesy, IRES IRB sends reminders to the investigator prior to the study's expiration date, notifying them that the study is due for a continuing review. Although courtesy reminders are sent, it is still the responsibility of the study team to submit the continuing review on time.

Continuing Review Requirements

- Research that is approved for a specified approval period cannot continue past the expiration date; If the protocol expires, all human research procedures must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of private identifiable information; All research and fund expenditures also must stop.
- To extend the approval period, create and submit a continuing review request in IRES IRB **60 days** prior to the study's expiration to ensure adequate time for IRB review;
- The expiration date of the protocol can be found in the main study record or in the latest IRB approval letter;



Purpose of the Continuing Review

- The purpose of the continuing review – to determine whether the study continues to meet approval criteria and all other applicable local requirements related to human subjects research e.g., compliance with training;
- The IRB will consider any relevant information received since the date of the last IRB review and approval e.g., Data Safety Monitoring Board recommendations, relevant publications, etc.;
- The IRB will review to assess whether or not the study's risk/benefit ratio is still favorable
- The IRB will also review subject enrollment to ensure that the study is likely to achieve the research goals (if enrollment is not proceeding as planned, the IRB may question whether it is ethical to expose additional participants to risks if the research is unlikely to yield meaningful results)

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Submitting CRs in IRES IRB

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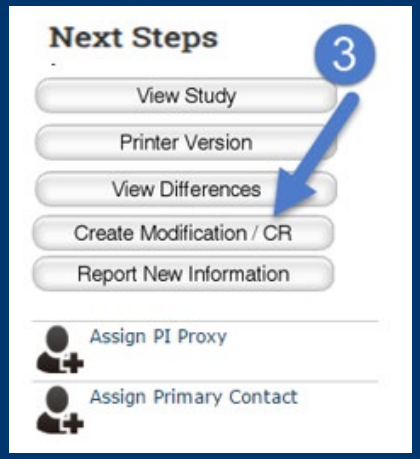
Submitting Continuing Reviews in IRES IRB

- A continuing review submission request is created from the main study workspace, as part of the Continuing Review action *(#3 below)*.
- If the continuing review also involves modifications to previously approved research, you can create a combined continuing review/modification submission.



Submitting Continuing Reviews in IRES IRB

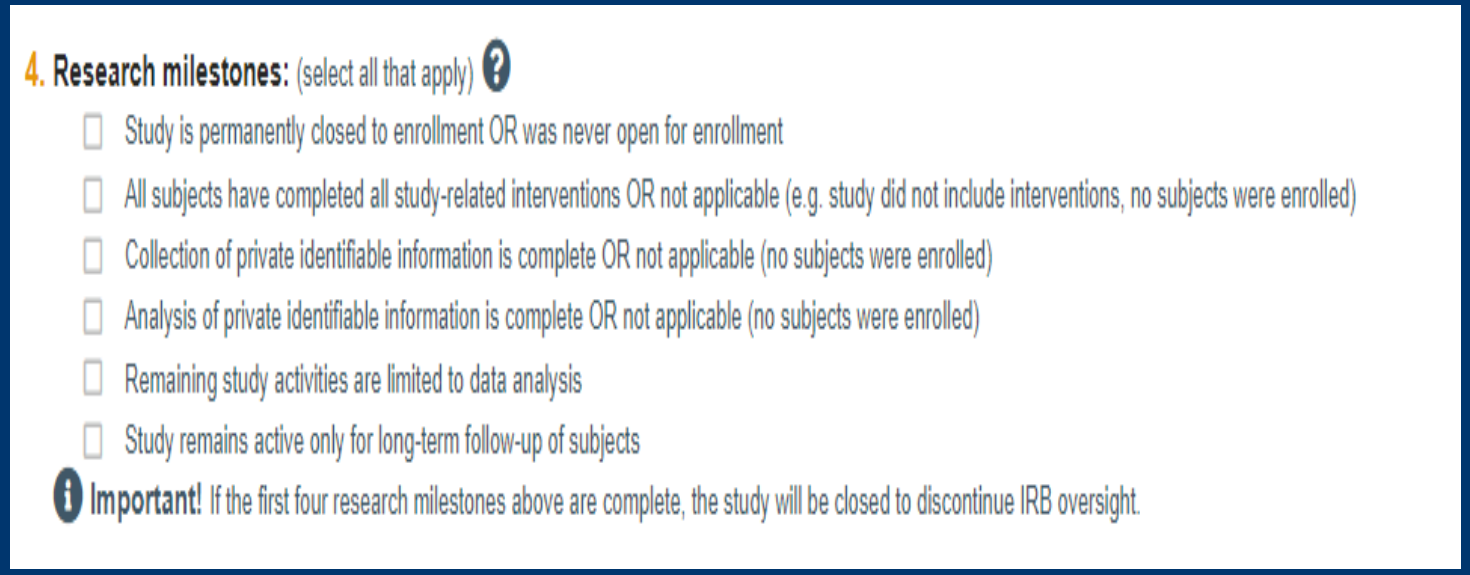
- Report enrollment totals as follows:
  - For the Yale site since the initial approval,
  - For the Yale site since the last approval (excluding MOD approvals and RNI acknowledgments),
  - Enrollment totals for multisite study. If the study enrolls only at the Yale site, then answers to questions 1 and 3 should agree.
- *Please click on "" for further Information.

HOT TIP:

- Provide a breakdown of enrollment if you are enrolling more than one subject cohort.

Submitting Continuing Reviews in IRES IRB

- Read the statements under the Research Milestones question. Check off all the true statements.



HOT TIPS:

- Read each option carefully, because some of the options contain two different statements.
- Study-related interventions are research interventions/procedures during the active enrollment and research procedures such as CT scans during follow-up.

- Long-term follow-up usually means record review, phone call, or survival follow-up.
- Provide the follow-up procedures that are ongoing if this box is checked

Submitting Continuing Reviews in IRES IRB

6. Check the items that are true since the last IRB approval for all sites involved in the study:

- [x] NO subjects experienced unexpected harm
- [x] Anticipated adverse events have NOT taken place with greater frequency or severity than expected
- [x] NO subjects withdrew from the study
- [x] NO unanticipated problems involving risks to subjects or others
- [x] NO complaints about the study
- [x] NO publications in the literature relevant to risks or potential benefits
- [x] NO interim findings
- [x] NO multi-center trial reports
- [x] NO data safety monitoring reports
- [x] NO regulatory actions that could affect safety and risk assessments
- [x] NO other relevant information regarding this study, especially information about risks
- [x] In the opinion of the PI, the risks and potential benefits are unchanged
- [x] All modifications to the protocol have been submitted to the IRB
- [x] All problems that require prompt reporting to the IRB have been submitted

- Under Question 7, attach any supporting documents. This includes an explanation of each item left unchecked above.

Possible Explanations

Statement that remains unchecked	Information to Include in Written Explanation
Anticipated adverse events have NOT taken place with greater frequency or severity than expected	Include an explanation of the difference between expected frequency or severity of the adverse events and the actual events that occurred, address impact on the subjects safety,
NO subjects withdrew from the study	Explain how many participants withdrew and why (if known), address whether the withdrawals may affect the targeted enrollment, if so, what actions will be taken to remedy it,
NO unanticipated problems involving risks to subjects or others	Explain any unanticipated problems since the most recent review and whether they have been previously reported as RNI submissions,
NO complaints about the study	Include the description of the nature of the complaints received for the study since the last Continuing Review (or initial review of the study), type of the complainants (e.g., participants, the clinic coordinators where the research recruits from, etc.), and how the complaints were resolved; if the complaint have bene previously submitted to the IRB via a Report of New Information, include the RNI#;
NO regulatory actions that could affect safety and risk assessments	For example, if there was a Black Box Warning related to drugs used in the study, include the information and explain the impact, reference the RNI#,
NO other relevant information regarding this study, especially information about risks	Include the description of the new information and references to literature describing the information e.g., articles that have been published on findings from other studies using the agent under study,
In the opinion of the PI, the risks and potential benefits are unchanged	If the risks or benefits should be assessed differently from the previous evaluation, explain the rationale. For example, if there have been recently published articles or results of other studies suggesting that the therapy under study is not beneficial or there have been new therapies approved for the condition of the participants that have not been previously available, include the references to the literature;
All modifications to the protocol have been submitted to the IRB	If there are modifications needed to the protocol that have not yet been submitted to the IRB, explain the changes and rationale why the submission have not been made and when the IRB should expect them,
All problems that require prompt reporting to the IRB have been submitted	If there are events that meet prompt reporting criteria have not been yet submitted, they should be submitted at the time of the continuing review, include the RNI number for the submission, or explanation why the events have not yet been reported to the IRB;

Best Practice - Research Progress Report

- In addition to explanations to items that remained unchecked in question #6, it's best practice to also provide information on the progress of the study, which may include the following:
    - The assessment of the recruitment efforts and whether enrollment is progressing as planned;
    - Description of the progress in each study arm;
    - Any reports about the overall study provided by the sponsor/coordinating center;
    - Any anticipated changes in timeline for completing data collection and analysis;
    - Confirmation that informed consent procedures are being followed appropriately;
    - Description of any challenges faced during the conduct of the study.

Continuing Review Process for Yale sIRB Studies

- Continuing Review is approved for the entire study, inclusive of all participating sites;

- There will be only one IRB approval letter for the study;

- You can combine the continuing review request with modifications butif site specific documents are affected by the change, a site modification will need to be separately submitted to each site;

Continuing Review Process for Yale sIRB Studies

There are two steps to submitting the continuing review report to the IRB:

1. Obtaining information from sites for continuing review report
    - You will need the following information from each of the sites:
        - Total enrollment # at the site,
        - Total enrollment # since the last approval (initial approval or last continuing review, whichever happened last),
        - Verification of whether certain statements are true for the site (Question #6 in the CR),
        - Any supporting information e.g., explanation of the progress,
        - Any additional comments about the study.
    - To obtain the information from the site, you can copy the table found in in Section 14.6 of the Investigator Manual and email it to the sites with a request to complete it.

Continuing Review Process for Yale sIRB Studies

2. Once you obtain the continuing review information from the sites, you will need to submit the report in IRES IRB.

- Report Continuing Review Data for the sites
  - In each site workspace, under Next Steps, click on Report Continuing Review Data. Transfer the information you received from the site. You can also upload any relevant documents received from the site.

- Create and submit Continuing Review for the study
  - Once the site information has been submitted, return to study workspace and create study Continuing Review as described earlier.
  - Note: Questions #1 and #2 apply only to Yale sites. Questions #3 and #4 apply to the overall study

IRB review outcomes

Decision	Meaning	Approved Documents
Approved	The study continues to meet approval criteria, new expiration date is assigned;	No watermarks are applied;
Modifications Required	The study continues to meet approval criteria but minor revisions are needed, the IRB letter might include a directive related to continuation of any activities e.g., recruitment of new participants may need to be paused until final approval is obtained but activities with currently enrolled individuals are allowed;	No watermarks are applied;
Deferred	The study may no longer meet approval criteria OR there is insufficient information to determine whether the approval criteria continue to be met e.g., if there is newly published data suggesting higher risks than previously believed;	No watermarks are applied;
Disapproved (Terminated)	Disapproval means that the study is no longer approvable and must be terminated. In case of regulated research, terminations must be reported to the federal agencies.	No watermarks are applied;

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Study Closures

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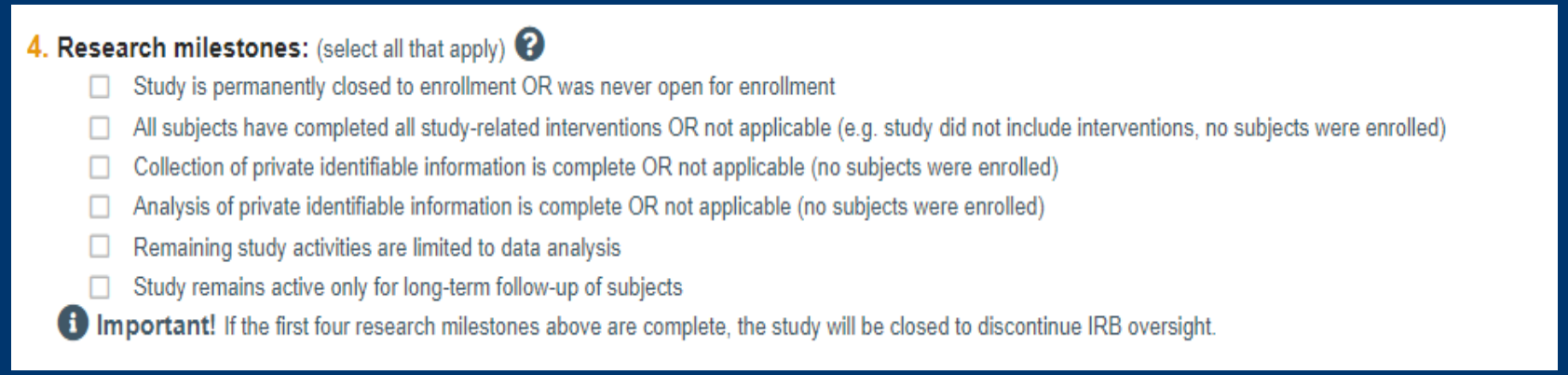
Study Closures

Research studies can be closed if all of the following criteria apply:

- The study is permanently closed to enrollment or was never open for enrollment,
- All subjects have completed all study-related interventions, including follow-up procedures (if applicable to the study),
- Collection of private identifiable information is complete (if any), and
- Analysis of private identifiable information is complete (if any).

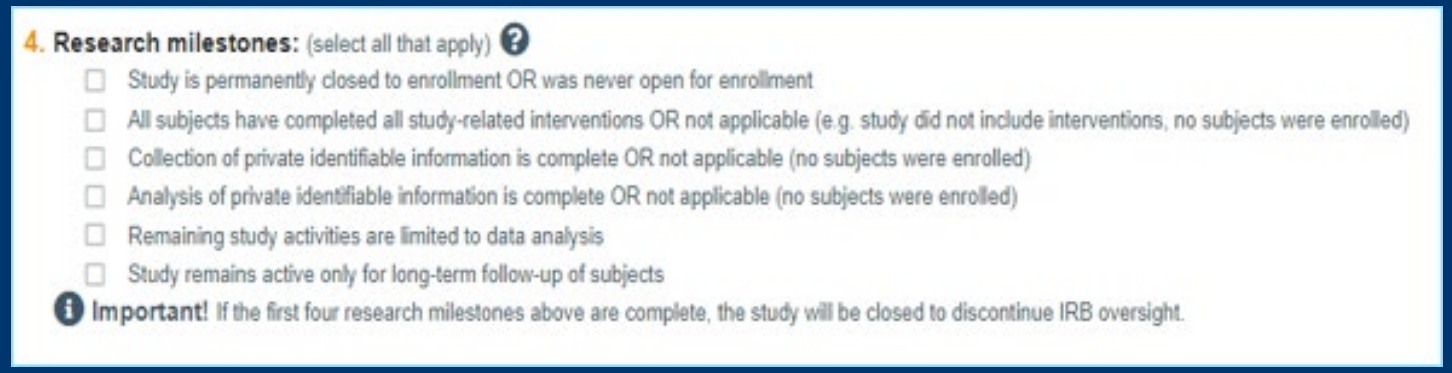

4. **Research milestones:** (select all that apply)

- ☐ Study is permanently closed to enrollment OR was never open for enrollment
- ☐ All subjects have completed all study-related interventions OR not applicable (e.g. study did not include interventions, no subjects were enrolled)
- ☐ Collection of private identifiable information is complete OR not applicable (no subjects were enrolled)
- ☐ Analysis of private identifiable information is complete OR not applicable (no subjects were enrolled)
- ☐ Remaining study activities are limited to data analysis
- ☐ Study remains active only for long-term follow-up of subjects

Important! If the first four research milestones above are complete, the study will be closed to discontinue IRB oversight.

Submitting Closures

- Create Continuing Review - if the first 4 statements are selected, you will be asked to acknowledge that the study will be closed by the IRB as it no longer requires IRB oversight



Note: once the study is closed, it cannot be reopened. It would need to be submitted as an initial application.

Additional Resources

- **HRPP Website**
- **HRPP Policy and SOP Manual:** This document serves as the Yale HRPP Policy and Standard Operating Procedure Manual which serves as a guide for all components of the Human Research Protection Program, including the Institutional Review Board, Investigators and their Research Teams, and other members of the Research Community.
- **Investigator Manual:** The HRPP Investigator Manual provides detailed information on research preparation, IRB submission, and study team responsibilities.
- **Quick Guides**: step-by-step instructions for all system actions in IRES IRB Help Center;

Additional Resources

- Training on IRES IRB System (Yale IRBs)

- Training on IRES IRB System (external IRBs)

Description: This on-line training session is designed for current and future PIs and coordinators of research studies under the purview of Yale IRBs. By the end of the session, the audience will gain an understanding of: - how to navigate the system; - how to submit protocols for initial and continuing reviews, - how to submit modifications and reportable new information, - where to find help.

Questions?

Questions? Contact HRPP@yale.edu
Yale HRPP Website

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