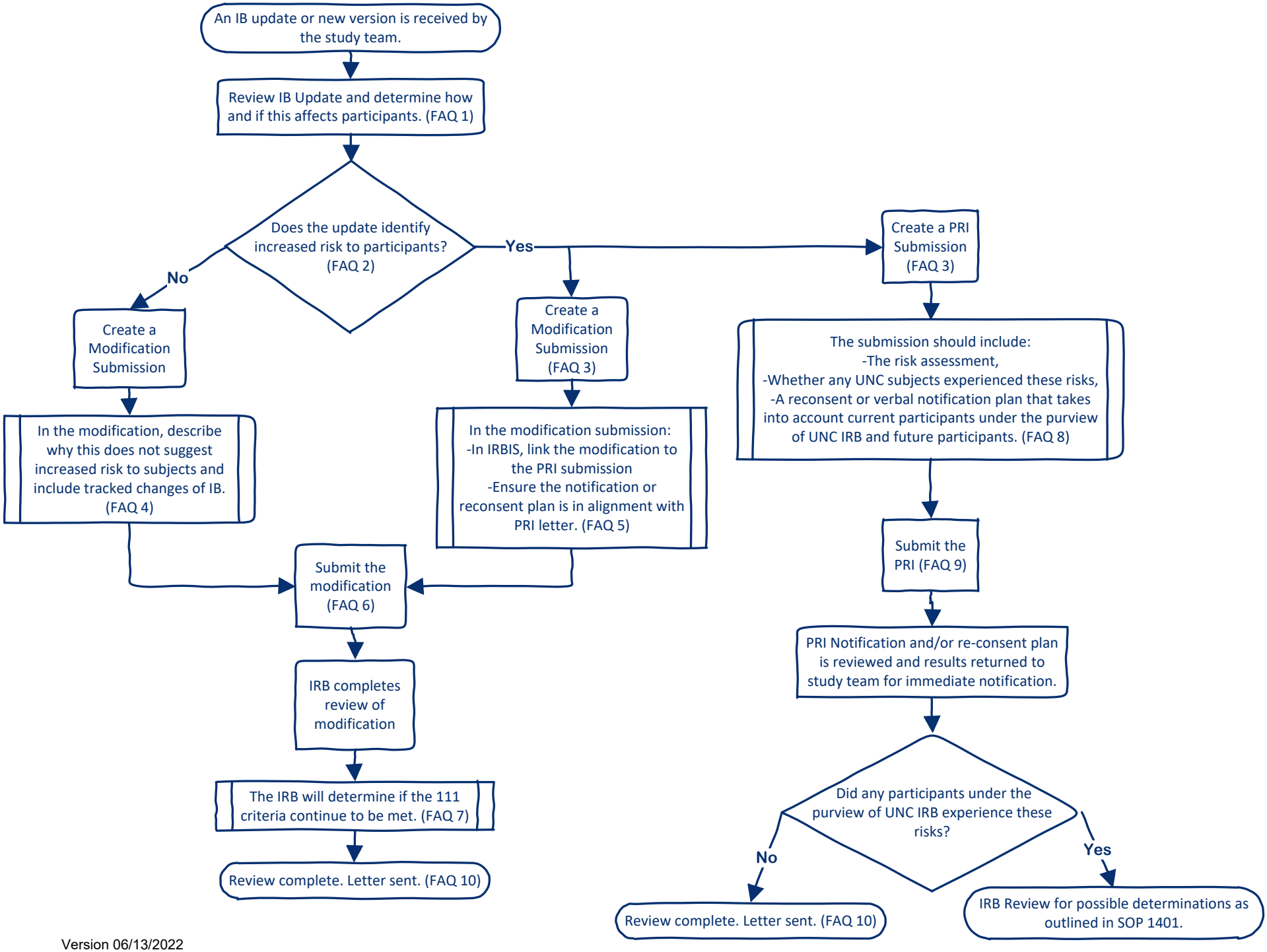
Investigator's Brochure Updates Flowchart



Investigator's Brochure (IB) Update – Frequently Asked Questions (FAQs)

1) What are some things to consider when reviewing IB updates?
    a. What are the changes?
        i. If the changes are administrative in nature and there are no additional changes to the risks of the study, submit the IB as a modification to the IRB and indicate that the IB changes are administrative and do not affect the risks of the study.
        ii. If new risks are identified or there are changes to the risk profile (i.e., a previously identified risk is identified as occurring at an increased rate), submit the IB update as a Promptly Reportable Information (PRI) report and as a modification.
    b. How does this affect the study?
        i. If the study is open to enrollment and actively recruiting participants include a plan for informing new participants of the new information prior to enrollment.
        ii. If participants are already enrolled and actively receiving Investigational Product (IP), include a plan for promptly notifying active participants of the new information.
        iii. If participants are in follow-up or off-study, consider if the risks are applicable to their status and include a plan to notify these participants of the new information.

2) Does the update suggest increased risk than was previously known to past, current, or future participants?
    a. The PI and study team are responsible for making this determination and taking into account their study population. The IP manufacturer's recommendations may be utilized as a guide when available.
    b. If yes, the IB update requires a PRI submission as well as a study modification.
    c. If no, the IB update should be submitted as a modification.

3) What is the timeframe for submitting the PRI and Modification if new risk information is identified?
    a. PRI reports should be submitted to the IRB within 7 calendar days of becoming aware of the new information.
    b. The PRI report and the modification may be submitted at the same time. The PRI event does not need to be resolved or noted prior to submitting the modification.
    c. Often a PRI event will need to be submitted prior to the modification to meet the 7-calendar day timeframe. If changes to the consent and protocol are required, these changes may take longer to implement, and the PRI submission will address prompt notification of participants, if applicable.

4) How should an administrative IB Update be described in the IRB modification?
    a. In the modification submission, indicate that the IB update includes changes that are administrative in nature and that no new risks have been identified and that the current risk profile has not changed.

b. If consent form changes are needed, i.e., risks were removed or risk frequency has decreased, ensure the consent form is updated and describe the changes in the modification description.
c. Attach a copy of the updated IB, a tracked changes version or summary of changes, and any relevant manufacturer's correspondence (i.e., a Sponsor's letter describing the changes and recommended reconsent plan, if applicable).

5) How should an IB update with risk changes be described in the IRB modification?
    a. Link the modification submission to the PRI submission for the IB Update.
        i. Respond "yes" that this modification is being submitted in response to New Safety Information.
        ii. Select the New Safety Information Reference ID for the related PRI submission from the list of available options.
    b. Describe the changes in the modification description, including any changes to consent forms.
    c. If the related PRI has already been reviewed, ensure the reconsent plan described in the modification matches the plan outlined in the PRI letter.
    d. Attach a copy of the updated IB, a tracked changes version or summary of changes, and any relevant manufacturer's correspondence (i.e., a Sponsor's letter describing the changes and recommended reconsent plan).
    e. Please ensure that all documents related to the IB update, i.e., the new IB, the tracked changes version, the revised informed consent form, etc., are submitted together as one modification.

6) What happens when the modification is submitted to the IRB?
    a. When the IB update changes are administrative in nature and there are no additional changes to the risks of the study, the modification may be meet the criteria for expedited review. The IRB will consider points from #7 below during the review.
    b. When new risks are identified in the IB update, the modification submission will receive full board review. The IRB will consider points from #7 below during the review.

7) How will the IRB review this information?
    a. The IRB will review the modification to determine if the 111 criteria for approval continue to be met and will consider:
        i. Does the study team's risk assessment seem appropriate,
        ii. Does this meet the criteria for expedited review,
        iii. Has the risk to benefit ratio changed,
        iv. If applicable, review the consent form to ensure it is consistent with the IB update,
        v. If applicable, ensure the reconsent plan from the PRI letter and the reconsent plan in the modification are in alignment,
        vi. Are there any other updates needed to reflect the change in the IB update throughout the application or protocol (e.g., risks section in application/protocol).

8) What information should the PRI submission include?
    a. The PRI form includes specific questions related to IB updates.
        i. Did the IB update change the risk assessment from what was previously approved?
            1. If yes, explain the identified risk changes.
            2. If no, consider if the IB update includes administrative changes only and does not need to be submitted as PRI.
        ii. Have any current or past subjects that are under the purview of UNC's IRB experienced these risks?
            1. If yes, please complete the full PRI report to describe the event(s) experienced by the subjects under the purview of the UNC IRB. These events could meet the criteria for an unanticipated problem involving risks to subjects or others (UPIRSO) as the participants experienced unexpected risks associated with the study.
        iii. Please provide a reconsent or verbal notification plan that includes current and past participation and onset of the risk in regard to the study-specific timeline or explain why reconsent or verbal notification is not applicable.

            (E.g., "Currently only subjects in long term follow-up are enrolled, and as these new risks are acute and occur within two hours of drug administration and our participants didn't experience these events they do not need to be notified." or "Currently we only have 2 subjects enrolled, and we will verbally notify existing subjects before the next drug administration and any newly enrolled subjects at time of consent and document the verbal notification and response in the research record."
        iv. Attach a copy of the updated IB, a tracked changes version or summary of changes if available, and any relevant manufacturer's correspondence (i.e., a Sponsor's letter describing the changes and recommended reconsent plan).

9) What happens when the PRI report is submitted?
    a. The PRI report will receive expedited review to ensure there is a plan for immediate notification of past, current and future participants of new risk information.

10) What needs to be done following IRB review?
    a. Study teams should review the final IRB letters. The Notification Plan in the IRB letter may not match what is submitted to the IRB.