

PENDING VS DEFER

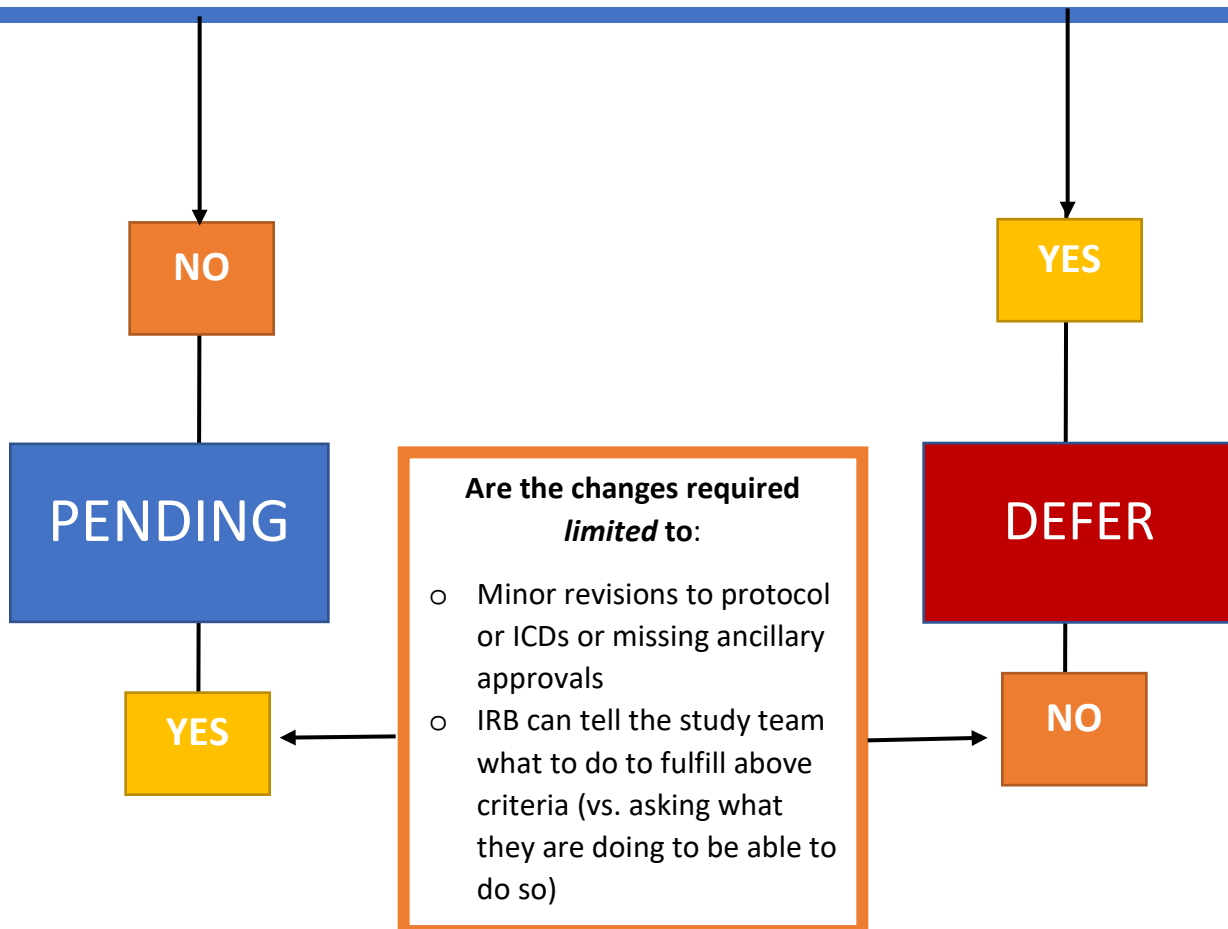
Does IRB request substantive modification or clarification to the protocol or informed consent (IC) that is directly relevant to any of the following criteria from 45 CFR 46.111 (DHHS) and 21 CFR 56.111 (FDA)?

If yes, check all that apply:

- Risks must be minimized
- Risks must be reasonable in relation to benefits, if any, and importance of knowledge to be gained
- Selection of subjects must be equitable
- IC must be sought from each subject/legal authorized representative (LAR) or waived
- IC must be documented or waiver granted
- Data will be monitored if appropriate for subject safety.
- Privacy & confidentiality must be adequately safeguarded

OR, if appropriate to the study, directly relevant to the following additional criteria from 45 CFR 46.111 and 21 CFR 56.111?

- *Additional safeguards for subjects who are vulnerable to coercion or undue influence (vulnerable populations) must be adequate*



Emory IRB Guidance

Some examples of required changes or clarifications that generally would preclude the IRB from approving the research¹:

Placebo Control Groups

- Providing a justification for using a placebo and withholding currently available treatment for a serious medical condition for subjects assigned to a control group (OHRP notes that in this example the IRB would need the investigator's response to make the determinations under 45 CFR 46.111(a)(1) and (2));
- Providing a description of procedures that the control group will undergo (OHRP notes that in this example the IRB would need the investigator's response to make the determinations under 45 CFR 46.111(a)(1), (2), and (4));

Enrolling Children

- Providing a justification for enrolling children in the research and an explanation of how the research would satisfy the requirements of subpart D of 45 CFR part 46 (OHRP notes that in this example the IRB would need the investigator's response to make the determinations under subpart D of 45 CFR part 46).

Change in Study Hypothesis/Design

- Revising the study hypothesis and, accordingly, the study design (OHRP notes that in this example the IRB would need the investigator's response to make the determinations under 45 CFR 46.111(a)(1), (2), and (4))

Assessment of Risks

- Providing clarifying information needed to assess the risks to subjects, such as clarifying whether individuals who have taken aspirin within 14 days prior to enrollment will be excluded from the study because of concerns about the risks of bleeding (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(1) and (2); see example 1 below for an alternative approach that would allow the IRB to approve the research with conditions).

Informed Consent Process

- Clarifying the timing and circumstances under which the informed consent of prospective subjects will be sought (OHRP notes that in this example the IRB would need the investigator's response to make the determinations under 45 CFR 46.111(a)(4); see example 2 below for an alternative approach that would allow the IRB to approve the research with conditions).

Revisions due to SAEs

- Providing a plan to implement additional subject monitoring to reduce risks to subjects, given the number of serious adverse events that have occurred in study subjects since the prior IRB review (OHRP notes that in this example the IRB would need the investigator's response to make the determinations under 45 CFR 46.111(a)(1), (2), and (4)).

Other issues – it depends!

- Board understands what the study goals are, but the submission must be heavily revised, as the protocol and consent forms need corrections, and the eIRB submission is inconsistent or incomplete: if the IRB fully understands the risks and benefits, and the study overall is low (though perhaps not minimal) risk, then a *very clear* but long list of required revisions could be “pending.” If any of the “unknowns” prevent the IRB from fully understanding the risks and benefits, or if the study is higher risk, “Defer.”

Example 1: Requiring that the investigator – to ensure that risks to subjects are minimized – add “a history of aspirin use in the past 14 days” to the exclusion criteria for subject enrollment in the research protocol, and designating an IRB administrator or other qualified IRB staff member to review the revised protocol and verify that the stipulated language was added to the exclusion criteria

Example 2: For a randomized clinical trial comparing two types of surgical procedures, requiring that the investigator – in order to ensure that informed consent will be obtained under circumstances that provide prospective subjects with sufficient opportunity to consider whether or not to participate – revise the protocol to indicate that informed consent of the prospective subjects will be sought by the investigator during an outpatient clinic visit at least one week before the surgery, and designating an IRB administrator or other qualified IRB staff member to review the revised protocol and verify that the requested language regarding the process for soliciting informed consent of the prospective subjects was added to the protocol.

¹ From OHRP Guidance: [Approval of Research with Conditions: OHRP Guidance \(2010\)](#)