IRB *EasyEd™* - For IRB Members Volume 1 Number 9

Topic: IRB Approval of Research with Conditions

Overview of the Topic

While the regulations do not explicitly address IRB approval with conditions, the Office of Human Research Protections allows for such IRB decisions, as does the FDA. In guidance, OHRP permits the IRB to approve a research study or proposed changes with conditions, and without further review at a subsequent meeting of the convened IRB, when those conditions are minor. In this case the IRB may designate the IRB Chair or other individuals with appropriate expertise or qualifications to review the response from the investigators and determine that the conditions have been satisfied. This allows the IRB considerable flexibility to approve the research with conditions and avoid the time delay associated with waiting for the next convened meeting of the IRB.

However, this is also one of the most problematic areas for IRBs, and a common finding in ORHP Compliance Letters, that IRBs approve research with conditions that are not minor. The key issue here is what is a ***minor*** condition and what is a ***substantive*** condition for which the response must be returned to the convened IRB for review and approval. First, let's define what a substantive condition is. OHRP defines a substantive modification as one that is directly related to the determinations required for approval at the HHS regulations at 45 CFR 46.111 and, if applicable Subparts B, C and D. In other words, if you need the response to the condition to make a required regulatory determination, the condition is not minor, as the convened IRB is required to ensure that the regulatory criteria are satisfied. Here are two examples ORHP provides as substantive modifications:

- Provide a justification for using a placebo and withholding currently available treatment for a serious medical condition for subjects assigned to a control group (this would be related to 45 CFR 46.111(a)(1) and (2)).
- Revise the study hypothesis and, accordingly, the study design (related to 45 CFR 46.111(a)(1), (2), and (4)).
- Describe the procedures that the control group will undergo (related to 45 CFR 46.111(a)(1), (2), and (4)).

Conversely, a minor modification is one in which the IRB requests that the investigator makes specified changes to the research or submits clarification or additional documents, and once that minor conditions are satisfied, the IRB considers the criteria for approval satisfied. Modifications are considered minor if they will not change the risk to the participant regardless of the response. OHRP provides the following examples of minor conditions:

- Confirm that the research excludes children.
- Submit certificates confirming ethics training.
- Precise language changes to informed consent documents (e.g. change "myocardial infarction" to "heart attack.")
- Substantive changes to protocol or informed consent documents along with clearly stated parameters that the changes must satisfy (for example, add the method of screening for pregnancy).

Here is a tip on conditions. Whether a condition is minor or substantive often depends on how the question is phrased. For example, "*Explain whether and why pregnant women are excluded from the research*" would usually be considered substantive. But if you change the question to an objective one, such as "*Confirm that pregnant women are excluded from the research*," it becomes a minor condition that can be easily evaluated. Or instead of requiring "*Add to the consent form a statement on whether or not research related injuries will be paid for*," which is not unambiguously minor, use a prescriptive requirement "Add to the consent form the standard language for research related injury found on page 11 of the IRB consent template," - no doubt minor. Usually if the condition requires a narrative response or involves an open-ended question and interpretation of whether it is met or not, it is probably not minor. On the other hand, if the condition is prescriptive or confirmatory, it is usually minor. Some of these determinations are difficult – it is always a good idea to document why you made the decision you did.

As mentioned earlier, a common finding in OHRP compliance letters is the following: "We determine that the [organization's] IRBs sometimes approved research at convened meetings contingent upon substantive modifications or clarifications that were directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111 without requiring additional review by IRB at a convened meeting." Here are some examples from letters:

- Provide a list of inclusion/exclusion criteria. What medications and conditions would constitute exclusion?

- Clarify what steps will be taken to minimize the risks as described to the IRB.
- How will the study instrument affect subjects?
- Provide information about how the new group of subjects would be identified and recruited.
- Explain why a standard randomized, parallel, positive controlled study design is not used for this study.
- Address the ethical considerations associated with withdrawing an FDA-approved medication from patients who are taking it prior to enrollment in the study.
- Clarify the intended use of the audiotapes and how data would be handled to ensure subject confidentiality.

Another issue is who is allowed to verify the minor conditions have been met. OHRP does not consider this verification to be review by the expedited procedures and thus it does not require an IRB member to conduct. This provides significant flexibility in assigning reviewers for conditions. Depending upon the nature of the conditions and the expertise and qualifications required, the IRB could designate the following individuals:

- The IRB chairperson
- Another IRB member or group of IRB members with particular subject matter expertise or experience
- A consultant with particular subject matter expertise who is not an IRB member
- An IRB administrator or other qualified IRB administrative staff person, who need not be an IRB member.

If the designated reviewer does not believe the conditions have been adequately addressed, the response must be returned to the convened IRB for discussion and further action.

While the investigator cannot begin the research until the conditions have been deemed met, the IRB can assign the date of continuing review based on the date the IRB approved with conditions, or the date the conditions were met.

When used appropriately, approval of research with conditions can be an effective way to facilitate the review process and reduce delays in approval. However, it is also a common way that IRBs are non-compliant. When approving research with conditions, make sure your IRB has a discussion of whether the conditions are minor or substantive, designate who is assigned to review and approve the response if minor, and document your decisions.

Reference: OHRP Guidance on IRB Approval of Research with Conditions, 2010

Questions for the IRB to Consider

Questions your IRB may ask when approving research with conditions:

1. Can the research be approved without conditions?
2. Can the research be approved with conditions?
   a. Are the conditions minor or substantive?
   b. Can the conditions be worded differently to make them objective or prescriptive and thus minor?
3. Who will be designated to review the response to the conditions?
4. **IRB Decision:** Can the research be approved with minor conditions and the use of a designated reviewer, or will the research be deferred to the next IRB meeting when the responses to the substantive conditions will be reviewed by the convened IRB?
5. Document whether the conditions are substantive or minor and who was designated to review and approve the conditions if minor. Assign the appropriate date of continuing review based on your organization's policy.

Case Studies

Would you consider the following conditions minor or substantive:

- Who pays for the tests?
- Provide the number of subjects that will be enrolled.
- What is the compensation range that participants would expect from participation?
- Add percentages of occurrence to each risk listed in the consent form.
- Will you be recruiting your own classroom students in the research?
- Confirm that you will not recruit your own patients in the research.

Prospective Thinking: As your IRB approves research with conditions, keep a list of those that were deemed to be minor and those which were determined to be substantive. Regularly review the list and check for consistency and correctness of determinations. Discuss any concerns that arise with the entire IRB.