wcg IRB

Changes in Research

What are They and When do They Need to be Submitted to the IRB?

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Changes in Research (CIRs) are one of the most common topics for inquiries that come to the Institutional Review Board (IRB). Two of the most frequent questions are:

1. Does the change we are planning require a full protocol amendment or can we just use an administrative letter?
2. Is this a change in research that requires submission to the IRB?

The primary regulatory guidance around CIRs for the IRBs requires that the IRB "[ensure] prompt reporting to the IRB of changes in research activity;" and that the IRB "[ensures] that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects." (21 CFR Part 56.108 (a), and similar language exists at 45 CFR 4.108 (a)(3)(iii))

Corollary to this are the responsibilities of the investigator as described in ICH GCP, which states that "the investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s))" (ICH GCP E6 R2 Section 4.5.2), and in

the federal regulations which state that if investigators wish to modify an ongoing IRB-approved research study, they must submit a request to the IRB and receive IRB approval before implementing the proposed modification, except where necessary to eliminate an apparent immediate hazard to subjects (21 CFR 312.66). If the investigators change the research in order to eliminate apparent immediate hazards to subjects without prior IRB approval, they should report those changes promptly to the IRB, in accordance with the policies of that IRB.

In this post we address these two questions and general guidance around CIRs, discussing what should be considered a CIR and where there is flexibility in the processes and regulations to decrease the administrative burdens but maintain compliance.

Does the change we are planning require a full protocol amendment or can we just use an administrative letter?

The documentation of a planned CIR must be clear and accurate. Anyone involved in the conduct of the research (researchers, review committee, future auditors) should be able to follow the changes and the rationale for the changes, including dating and version control as appropriate. The submission should include all the necessary information for the IRB to review the updates to determine if the changes continue to meet the regulatory criteria for approval and that the risks remain reasonable in relation to the anticipated benefits.

With regard to formatting of the actual CIR plan, sponsors or institutions may have policies for what kind of changes require a full, tracked-changes revision of the current protocol document and which changes can be documented by other means such as an administrative letter / note to file or in a document addendum or appendix. From the IRB perspective, the chosen format doesn't matter. If the documentation is clear and changes (and rationale for the changes) can be followed logically, the IRB can accept any reasonable format for the CIR.

If there are some study documents that don't require changes to match the submitted CIR, the submission should also make that clear to avoid questions about whether they are unintentionally missing from the submission. For example:

- Part A of the protocol is complete and closed to enrollment, and therefore the ICF for Part A is not being revised and the CIR only affects the informed consent for Part B participants.
- The amendment describes a new sub-study that not all sites will participate in, therefore not all sites will need the additional ICF.

Based on what is being changed, the CIR submission may require additional

supplemental documents, such as:

- Package inserts and/or investigator brochures for any drugs or biologics that are being added to the study.
- Appropriate FDA documentation, instructions for use and or device brochures for any new medical devices.

Is this a Change in Research that requires submission to the IRB?

All changes in research must be reviewed and approved by the IRB "before implementing the proposed modification, unless the change is designed to eliminate an apparent immediate hazard to subjects" (45 CFR 46.103(b)(4)). "An immediate apparent hazard to subjects" is generally considered a situation in which action must be quickly taken during the study to prevent or to treat a significant possible adverse event, in a way that may not be consistent with the protocol (for example, it may require the use of a protocol-prohibited medication). When actions are taken to prevent immediate apparent hazards, they should be promptly reported to the IRB, with any the documentation of resulting changes in the protocol or consent such as new safety assessments.

Aside from those urgent situations, all changes to the research plans must be submitted to the IRB, reviewed, and approved by the IRB before

the changes can be implemented. This applies not just to the protocol and consent documents but to all other materials that comprise the study documents and study plans. See the box below for a list of other documents, information or study policies that would also require IRB review and approval before they can be changed.

When CIRs are received, the IRB will assess the planned change and the context and rationale and will determine whether the changes represent no new risks for study participants (in which case the CIR review can usually proceed through the expedited review pathway), or the changes represent new risks, in which case the CIR must be reviewed at a full, convened IRB meeting. Making sure that CIR submissions include all necessary and contextual information such as the rationale and reason for the changes, and the current status of the study, can facilitate the review process and avoid questions from the reviewers, and may lead the IRB to suggest administratively easier processes. For example, if there is new risk information in a study which has participants on a study drug but is no longer recruiting, providing participants with a short addendum to the informed consent document focused on the new information may be easier and more appropriate than a revision of the full initial informed consent document.

Summary

CIRs are common and expected during a clinical study. While the regulations are clear that any changes to the proposed study plan (not just the protocol or consent documents) must be reviewed and approved by the IRB in advance, there is flexibility in the formatting and administration of how these changes can be designed and submitted to reduce the burden on research teams and to make the information as clear as possible for research sites and participants. IRBs are happy to discuss upcoming CIRs with research sponsors, to help determine the most appropriate and efficient preparation and submission of the information.

Changes to the following study documents, study information or policies require IRB review:

- Study protocol (by amendment, administrative letter, or any other format)
- Informed consent document or process
- Participant recruitment plans including payments related to recruitment efforts
- Participant-facing materials — recruitment materials (advertisements, brochures, social media posts, scripts and story boards), participant retention materials, diaries, ID cards, etc.
- Payment to participants (reimbursement, compensation or incentive payments)
- Study documents that have been translated into a new language (or request for translation provided by the IRB)
- Waiver of HIPAA authorization
- Changes to previously-submitted financial interest disclosure
- Change of principal investigator or site research personnel (for site approvals)
- Change in address or contact information for a research location

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