

Completing the Health Sciences IRBs Change of Protocol Form Guidance

Please also see the instructions for the submission of a Change of Protocol Form that are posted on the Health Sciences IRBs website at www.medicine.wisc.edu/irb.

Presentation of changes of protocol can be one of the biggest challenges for researchers. Effectively communicating to the IRB what will be changed, why the changes are being proposed, how the revisions alter the IRB-approved protocol, and the impact of the changes on the risk/benefit ratio of the study reduce modification requests from the IRB and shorten IRB review time. This document was prepared to help researchers present clear and complete descriptions of changes of protocols.

Section A

This section provides the first identification of the documents that have been affected by the change. The IRB staff use this section as a guide to how changes are described in the IRB approval notice.

- If a formal protocol has been developed for the study, the revised version of this document should be submitted along with the change form. The changes made should be highlighted or tracked in some way so that the IRB can easily compare the previous version of the protocol with the revised version.
- If the changes of protocol affect the information previously provided to the IRB in the Initial Review Application that was approved, this document should be revised to ensure that it continues to accurately describe the protocol. Updating the Initial Review Application, especially the Study Description section, is particularly important when no formal protocol was developed or when information in the formal protocol affects local procedures.
- Inclusion of a version number and date on the amendment or revised Initial Review Application is essential to assist the IRB and the research team in tracking changes to documents. Please ensure that the version date of revised documents is noted on the Change of Protocol form.

Section B

This section alerts the IRB to the types of changes that are being proposed. The description of the specific changes provided in Section C of the form should be written to clearly address how the changes affect the areas of the protocol that were identified as being affected by the revisions.

Section C

This section is the most critical component of the submission. Some of the most effective change of protocol submissions the IRB receives are those that break down the changes into categories of changes and then provide a rationale for each change. See Appendix 1 for an example of this approach. All five points in this section need to be addressed. Specific guidance regarding how to address each of these points follows.

1. The substantive (non-administrative) change(s) being proposed.

GUIDANCE: A detailed account of the changes is critical. Reliance on a study sponsor's description of the proposed revisions is not recommended, because they often do not provide the specificity the IRB needs to assess the changes. However, it is also not helpful just to provide a list of changes even if reference is made to a specific section of the protocol that is revised. It is best to organize the changes by category and describe all changes relating to that overall type of revisions. For example, the revisions could be categorized and given subheadings to indicate the general nature of the changes, such as "REVISED ELIGIBILITY CRITERIA", "UPDATED TOXICITY MONITORING", "ADDITION OF SITES", "INCREASE IN ENROLLMENT NUMBER". This section should describe substantive changes to the protocol. Administrative changes should be described in Section E.

2. The rationale for each of the change(s)

GUIDANCE: It is helpful to provide an overall rationale for all of the proposed changes, if one exists, and to describe the specific rationale for each type of change being made. For example a change submission might describe that several revisions to the protocol are being made to increase subject monitoring based on new risk information gleaned from sponsor safety reports and then specifically note changes in laboratory tests conducted and eligibility criteria that are now included in the sponsor protocol.

3. How the current method or procedure in place will be altered by the change

GUIDANCE: Describe what was previously approved by the IRB and how the changes alter what the IRB approved. For example, if the number of subjects will be increased, describe how many subjects were previously approved by the IRB, how many more will be enrolled as a result of this change, and the statistical justification for this change in subject number. Or, if additional monitoring will be added, describe the monitoring in place before and whether the change will alter the timing, length or number of study visits (e.g., "Previously subjects had ECGs every six months; two additional ECGs are being added, one to visit 4 and one to visit 8 to monitor for possible cardiac toxicities...")

4. Whether the proposed change(s) potentially affect the risk/benefit ratio of the study

GUIDANCE: Describe in this section whether the changes will present any new risks or increase risks to subjects (either as the result of a new risk or exacerbating a risk already present), have no effect on risks to subjects, or decrease risks to subjects. If new or increased risks are identified describe whether the benefits to subjects offset these risks. In the case of therapeutic research, it may be that new risks are identified but given the nature of the subjects' disease and their limited treatment options the potential subjects may still be expected to directly benefit from the protocol treatment. In the case of non-therapeutic research, any significant increase in risks needs to be well-addressed especially to demonstrate that the societal benefits of the research are critical.

This section should also address any changes in design or sample size that would affect whether the study's objectives can still be met. If substantive changes in study design are being made, please provide a new statistical justification, describe how data collected before this change will be incorporated into analyses, and address why the study should continue.

5. Why the proposed changes will or will not affect the risk/benefit ratio

GUIDANCE: When describing the potential impact on subjects of the changes provide support for the assessment. For example, if it is concluded that there is no effect on the risk/benefit ratio explain why no effect would be expected.

Section D

If the change involves new information that should be disseminated to subjects, describe this in this section, including how the information will be provided to subjects (e.g., via telephone, letter or consent form addendum) and the timeframe within which the information will be disseminated to subjects (e.g., they will be informed within 1 month or by their next study visit, whichever comes first). New information that could affect subjects' willingness to participate in a study or information that describes new risks that are life-threatening or result in permanent disability should be provided to subjects promptly. Copies of revised consent and assent forms and/or addenda to the consent form should be submitted, with the changes highlighted or underlined, along with the change of protocol.

If it is not expected that subjects will be re-consented, explain why the change does not represent new information that would affect subjects' willingness to participate in the study or significant new risk information. If all subjects have completed study treatment, only information about potential late effects (e.g., increased rate of cancer) would be expected to be provided to subjects.

Section E

Administrative changes made to the protocol should be described in this section and not in Section C. Copies of a revised protocol or amendment and cover letter from the study sponsor may be submitted in lieu of a list of changes.

Section F

Generally, the IRB requires the principal investigator (PI) to sign submission to the committee. If the PI is unavailable, a co-investigator may sign or someone who has primary medical oversight responsibility for the protocol.

APPENDIX 1

Example for the presentation of a change of protocol

CHANGE IN EXPERIMENTAL GAS DOSING: We propose to broaden the options for use of a third dose of an experimental contrast gas for MRI imaging (Visit 2 and 9).

Rationale: The technology and hardware used to acquire the MR images is relatively new, and there have been instances when unanticipated failures have led to lost data. When this happens, the researchers would like the option to use a third dose of the experimental contrast gas rather than repeat a scan. The faster imaging will allow a shorter breath hold time and has been previously tested on normal volunteers. It is necessary to validate the newer technique in patients with lung disease so that it can be compared to existing imaging sequences. The use of the third dose of the experimental contrast gas will extend the total exam time by 10 minutes (see revised consent form) to allow for additional preparation time of the gas and scanning.

Effect on risk/benefit ratio: The proposed change should have no effect on the risk/benefit ratio. Previous protocols at this site (IRB number 2000-XXX, 2001-XXX) and at other sites have used three doses of the experimental contrast gas in smoking and non-smoking subjects, and in patients with a wide range of diseases, including asthma, chronic obstructive pulmonary disease, and cystic fibrosis without serious adverse events and no respiratory-related adverse events. The risk due to the use of the experimental gas already exists in the current protocol and is addressed by continuous monitoring of ECGs and blood oxygen saturation. There is no increased risk to subjects associated with the additional inhalation of the gas assuming adequate recovery of between breath holds; the current 5-10 minute gap between scans to prepare each dose of the gas should provide adequate recovery time. We have scanned more than 60 subjects for this present protocol with no respiratory-related adverse events. The procedure description has been modified in the protocol to include the option third dose of the gas.

CHANGE IN STUDY VISITS: We wish to expand visit window for resolution visits to accommodate the occasional subjects who do not resolve their cold symptoms within 6 weeks of the acute infection they undergo for this protocol.

Rationale: There are individuals who do not resolve their cold symptoms within 6 weeks of an acute respiratory infection. We would like to obtain resolution assessments at a time when cold symptoms have resolved so that these assessments can be used as a baseline for the acute cute assessments.

Effect on risk/benefit ratio: No effect, may increase scheduling inconvenience. The protocol and consent form have been revised to include the potential need to delay the resolution study visit.