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Human Research Protection Program Training

Modifications and Continuing Reviews

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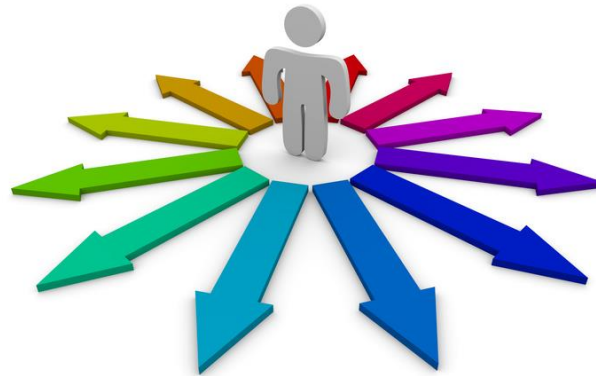
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Modification Overview

Generally, all changes to a study, even minor ones, must receive IRB approval before they are implemented.



Modification Approval Exception

- The *only* exception to the requirement for prior IRB review and approval is when the changes are “necessary to eliminate apparent immediate hazards to the subject” (45 CFR 46.103.b.4, 21 CFR 56.108.a).
- In such cases, the actions taken should be reported to the IRB within 5 working days, and approval should be sought for permanent changes to prevent the hazards in the future.



Modifications to Exempt Studies

For Exempt research **ONLY**, researchers can make minor changes to the study without notifying the IRB. However, significant changes must be submitted.

Examples of Significant Changes (Submit to IRB)

- Adding new subject population/procedures
- Adding new funding source
- Adding questions that are sensitive in nature
- Any change that makes the study no longer Exempt
- Change in PI
- Disclosing new financial interest

Examples of Minor Changes (Do Not Submit to IRB)

- Editorial changes to consent
- Adding non-sensitive questions
- Adding questions that are sensitive in nature
- Adding standard recruitment materials
- Increasing/decreasing number of subjects
- Personnel changes (not PI)

Types of Modifications



3 Main Categories

- Administrative Modifications
- Minor Modifications
- Major Modifications

1.6 * Types of changes being made (check all that apply): **(REQUIRED)**

- Making changes to PI or personnel
- Adding a new funding source
- Adding sites
- Increasing enrollment numbers
- Request for single subject exception
- Making changes to imaging or procedures that involve radiation exposure (X-rays, CTs, DEXA,
- Modification to follow subject or subject's partner who became pregnant on study
- Other changes, such as changes to recruitment, procedures, risks, etc.
- Changes that don't affect the IRB application or documents

Administrative Modifications

Definition: Changes that do not affect study subjects in any way.

Examples:

- Changing key personnel
- Adding funding
- Changing sample handling procedures (i.e. method of shipping samples)
- Fixing formatting or typographical, grammatical, or spelling errors to the application or consent form



Minor Modifications



Definition: Changes to previously approved research in which:

- any change in risk to participants is no more than minimal, and
- all additional activities or procedures would be eligible for review using the expedited procedures if submitted as part of new research, and
- either the research itself involves minimal risks or the changes do not significantly alter the study design.

Minor Modification Examples

- Changing procedures, activities or study design without adding more-than-minimal risks
 - adding blood draw or other non-invasive procedures
 - adding additional follow up questionnaires
- Changing recruitment methods or revising questionnaires
- Changing language in the consent forms for better clarity
- Adding subject populations (even vulnerable populations- i.e. minors, patients unable to consent) *as long as risks remain minimal* and other criteria for expedited review are still met
- Reducing risks
- Changing PI for Expedited or Exempt study
- Changing PI for Full Committee study if new PI has same level of expertise

Major Modifications

are changes to previously approved research in which

- Any increase in risk to participants is more than minimal
or
- any additional activity or procedure would not be eligible for expedited review if submitted as part of new research
or
- the research itself involves more than minimal risks and the changes significantly alter the study design.

Major Modification for Full Committee: Studies: Examples

- Changing, adding, or deleting drugs, devices, or other treatments being studied (significant alteration of design of study)
- Adding or deleting major procedures or diagnostic tests (e.g., adding bronchoscopy or spinal tap; doubling duration of treatment; deleting adjuvant chemotherapy; deleting diagnostic MRI or liver function test)
- Increasing major risks or discomforts (e.g., risks from new procedures, deleted safety measures, or newly discovered serious risks; risks that are serious by themselves do not become minor even if subjects already have a terminal disease)

Major Modifications for Expedited Studies: Examples

- Adding invasive procedures other than small-volume blood draws
- Adding use of experimental drugs or devices
- Adding serious privacy risks (e.g., asking participants about abusive behavior or illegal activities)
- Revising questionnaires- if the new questions are more likely than the old ones to evoke responses that would reasonably place subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing if the answers became known outside of the study context

What to Submit to the IRB for Modifications

- Modification Form indicating *type of modification* and *what is being changed*
- Revised versions of all previously submitted Consent Forms or Other Study Documents
- Additional documentation needed to explain or implement the modifications
 - Sponsor's protocol or correspondence
 - Investigator's Brochure
 - Letters of support
 - New questionnaires
 - New Consent Forms (if new population is being added)

Types of Review for Modifications

- Administrative and Minor Modifications are reviewed by “Expedited” procedures (individual committee members)
- Major Modifications are reviewed by “Full Committee” review (convened board meeting)
- Modifications for Exempt studies get a “re-certification” of their Exempt status

Things to Remember for Modifications

- Answer **ALL** questions on the Modification Form
- Only check “Major Modification” if changes are significant and require Full Committee Review (review the guidance before submitting and call IRB staff if needed)
- Expiration date **does not** change (unless modification is combined with Continuing Review)
- Approval letters sent out when approved

Additional Tips for Modifications

- If modifications *significantly* alter study design and study aims- better to submit as a new study rather than a modification
- Provide detailed description in the modification form of all changes being made and what documents are changing
- Allow at least 2-3 weeks for review of Expedited modifications and 4-6 weeks for review of Full-Committee modifications

What would you do if...

you currently have an expedited (no subject contact) application approved for a study that involves retrospective medical record review of patients visiting an outpatient clinic for back pain. The PI now wants to modify the study to conduct a survey with a small subset of patients. The survey does not include any questions that might increase risk to the subjects.

- What type of modification request would you submit?
- What would you need to include in your submission?

What would you do if...

you currently have an approved Full Committee study that involves a Phase I drug. The PI now wants to add an extra blood draw (10 ml) for pharmacokinetics (PK) one hour after the first infusion of the study drug.

- What type of modification request would you submit?
- What would you need to include in your submission?

What would you do if...

you currently have an approved expedited review study that involves conducting anonymous surveys at fast food restaurants. The PI now wants to include subjects under 18 years of age.

- What type of modification request would you submit?
- What would you need to include in your submission?

Continuing Review (Renewals) Overview

Re-review of all projects involving human subjects is required at *least* annually (see 45 CFR 46.109(d) (DHHS) and 21 CFR 56.109(d) (FDA))



Continuing Reviews- General Info

Re-review of all projects involving human subjects is **required at *least* annually** (see 45 CFR 46.109(d) (DHHS) and 21 CFR 56.109(d) (FDA))

- even if no changes are made,
- even if the only study activity is patient follow-up, and
- even if the only study activity is data analysis.

- ***Exception to annual review*** – The IRB may grant up to a 3 year approval for expedited studies without Federal funding or oversight

- The IRB may require review more frequently.

Continuing Reviews- What if my study expires?

If Approval Expires, ALL ACTIVITIES INVOLVING SUBJECTS (AND IDENTIFIABLE DATA) MUST STOP.

- The only exceptions being activities needed for participant well-being or subject safety
 - You should notify the IRB before any such research activities are done (if possible)
- No new subjects may be enrolled
- No study visits or data collection should take place (except if needed for safety reasons)
- Submit Continuing Review Form as soon as possible!

What to submit for Continuing Reviews

- Continuing Review Form indicating study and enrollment status
- All Consent Forms that are currently being used ***even if there are no changes***
- If modifying study with continuing review, submit **revised** versions of the IRB application and other documents ***only*** if these are being modified at the time of the continuing review.
- Audit or Data and Safety Monitoring Board Report *(if a report was issued)*

Continuing Review: Type of Review

- Full Committee Review
 - New studies with *Greater-Than-Minimal Risk*
 - All *major* modifications
 - Renewal of Full Committee studies with *ongoing* subject contact
- Expedited Review
 - New studies with Minimal Risk AND fall into one of the Expedited categories.
 - Continuing Reviews for Expedited studies
 - Minor Modifications (for both Expedited and Full Committee Studies)
 - Continuing Review of Full Committee studies that qualify for expedited review (no ongoing subject contact or limited to minimal risk activities)
- No Continuing Review needed for Exempt studies

Full Committee Studies Renewed through Expedited Review:

Studies Initially Reviewed as Full Committee can be reviewed under the Expedited Review procedures if one of the following apply:

- The research is permanently closed to the enrollment of new subjects and the research remains active only for long-term follow-up such as medical records review and telephone follow-up. (If one of the research follow-up procedures is an intervention such as a blood draw or an x-ray, the renewal is not eligible for expedited review).
- No subjects have ever been enrolled and no additional risks have been identified since the last Full Committee review.
- The Full Committee determines the study involves no more than minimal risk and agrees that the study can undergo expedited review in the future.

Continuing Review – Data Analysis Only:

Studies Being Renewed for Data Analysis Only undergo expedited review

- “Data analysis” means analyzing data only. It does not include the collection of data from medical or other records and does not include analyzing specimens
- It is acceptable to include minor or administrative modifications. A major modification would be unlikely if the study is truly in data analysis.
- No consent forms or other documents related to subject contact should be submitted unless required by sponsor.

What would you do if...

you have a currently approved Full Committee study and the P.I. receives an updated sponsor's protocol that identifies additional risks to the study or includes a change in the wording of a previously identified risk?

- What type of modification request would you submit?
- What would you need to include in your submission?

What would you do if...

you currently have an approved study that takes place at Parnassus and Mt. Zion. The PI now wants to add the VAMC as a study site.

- What type of modification request would you submit?
- What would you need to include in your submission?

Common Problems with Modifications:

- Not all changes are stated explicitly in the submission form
- Affected documents are not attached with submission
- Changes are not made to all affected documents
- Comparing wrong version of the application (i.e., not the currently approved version)
- Multiple submissions are sent to the IRB at the same time or before a prior submission has been approved

Common Problems with Continuing Review Submissions:

- Continuing Review form is not complete (i.e, “summary of results” or “plans for the coming year” are left blank)
- Subject numbers do not add up and no clear explanation is given.
- Study status (Section 2) does not agree with other parts of the form
- Required consent forms and other revised documents are not attached
- If the study has expired, assurance that no study activity will occur and explanation of approval lapse including a corrective action plan is not given plan.

Additional Instructions for all Modifications

- To facilitate review, specific changes in the revised version of the application, consent form(s), and other documents must be summarized in the modification form or the modification section of the Continuing Review form.

It is extremely helpful if the specific sections of the application and consent documents are referenced.

- All revised documents should be revisions of the version most recently approved by the CHR.
- All revised documents should include a new version date.

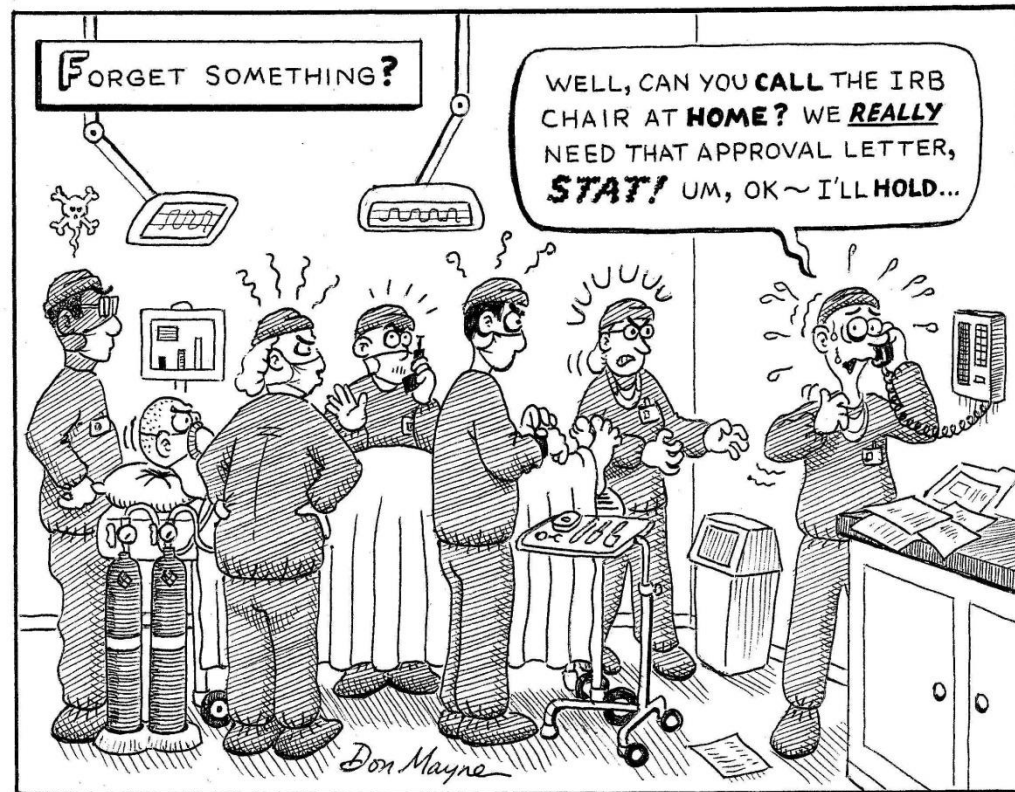
Additional Tip:

- **DO NOT attach documents with “tracked changes.”** Researchers, IRB staff and committee members can identify changes between versions of the application, consent documents and other attachments by using the compare documents feature in iRIS.

Note: The compare documents feature only works for WORD documents and the CHR application.

Remember!

IRB Review is required before **initiating**, **modifying** or **extending** any research project that uses human subjects



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Questions?

www.research.ucsf.edu/chr/

- **Call or email the analyst assigned to your submission**
- **Call or email the Analyst of the Day**
- **Main IRB Line: 415-476-1814**
- **Main IRB Email: irb@ucsf.edu**

