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MD Anderson Cancer Center
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Policy on IRB Revision Procedures to Previously Approved Research Protocols

SCOPE

This policy applies to IRB review of changes to research under the oversight of the MD Anderson Institutional Review Board (IRB).

PURPOSE

The purpose of this document is to provide guidance to investigators on how to identify, classify and submit changes to previously approved research protocols by an IRB. The document also provides guidelines to assist the IRB with review of these changes based on human subject protections regulations and FDA regulations at 45CFR§46.110 and 21CFR§46.110, respectively (Regulations).

PROCEDURE

Any changes to currently approved research must be approved by an IRB prior to implementation. The Regulations permit an IRB to review changes to previously approved research using an expedited review process only if such changes constitute minor or non-substantial changes in the previously approved research. Changes that do not meet the criteria for expedited review will be reviewed by the convened IRB.

EXAMPLES

The following tables describe the types of review an IRB may use when reviewing changes to previously approved research.

Table 1. IRB Review Type Based on Initial Review of Protocol

Protocols Initially Approved by Expedited Review Process that *May* Be Reviewed as Expedited	**Protocols Initially Approved by Convened IRB Review that *May* Be Reviewed as Expedited**
• The change poses no more than minimal risk to subjects. • Any added procedures must fall within Categories (1)-(8) of research that may be reviewed using the expedited procedure.[1] [1] *Click on this link to visit the OHRP website on Expedited Review Categories:* OHRP Categories	• Changes do not pose an increased risk to subjects; AND • Changes constitute a minor change to previously approved research (see examples below). • Any added procedures must fall within Categories (1)-(8) of research that may be reviewed using the expedited procedure.

The tables below include examples of changes to research that are routinely submitted to the MD Anderson IRB, as well as the type of review procedure the IRB is required to use to review the change. These tables may be used as guidance by researchers (this is not an exhaustive list, only examples). However, the IRB will make the final determination as to the appropriate review level.

Table 2. Examples of Changes that may be reviewed using the expedited review procedure:

Research Staff Changes

- A change in research staff, including the roles of PI, Co-PI, Collaborator, Research Nurse, Manager, Contact Person, is a minor revision under the following circumstances:
  - the change does not alter the competence of the research team,
  - the staff member has the necessary credentials, and
  - the staff member has the required human subject protection training.

- Addition of investigative site. For PI initiated protocol, it is the responsibility of the PI to conduct a feasibility review to ensure site PI and site research team has human subject protection training and the appropriate resources. For protocols that are industry sponsored, the responsibility is that of the sponsor.

Protocol Changes

- Amount or frequency of blood draw that is within the IRB and institutional policy limits (Institutional Blood Volume Collection Guidelines (see Institutional Policy CLN0508)
- Extension of the follow-up period where no research-required/related invasive procedures will be carried out during such extended follow-up period
  - safety of patients is maintained
  - study integrity is not compromised
- Minor increase or decrease in sample size with adequate justification
  - number to be “treated” remains the same, and
  - the change does not affect the statistical analysis
- Dates of data collection
- For a retrospective chart review, it is likely that even a substantial increase or decrease in sample size should be considered a minor revision.
- Increase in MD Anderson accrual where maximum accrual at all sites remains unchanged

Informed Consent Changes

- Adding risks, or change in wording, that does not alter the risk/benefit ratio, or impact the participant’s willingness to continue to participate in the study
- Does not alter the content and consists of:
  - template updates
  - fixing typos
  - edits to informed consent language to improve readability or to improve clarity
- Minor change in remuneration for participation in the research (Note: Description of remuneration should be consistent in all protocol documents and contracts, and is required to be reviewed by the IRB. You can review the IRB Policy on Remuneration here.)

Addition of the following types of appendices

Changes that do not fulfill the above criteria will require review by the convened IRB.

- Questionnaires
  - Standard quality of life (QOL) questionnaires that do not substantially increase participation time and burden
  - Removal or addition of non-sensitive questions from previously approved questionnaire(s)
- Advertisement or recruitment material (not coercive in nature) or locations where advertisement or recruitment material will be posted or distributed

Miscellaneous

- Edits/changes to correct discrepancies or typographical errors within protocol documents such as accrual numbers, duration of research procedures, participating research sites
- Protocol exceptions for a single patient
- Replacing accrual slots to account for patients that failed eligibility during the IRB-approved screening phase of a protocol

Table 3. Examples of Changes that WILL be reviewed by the convened IRB:

Protocol Changes

- Change in protocol including changes in/to:
  - Design
  - Addition of a new diagnosis or cohort or expansion cohort
  - Addition of a new phase of trial (not already planned for in the initial design) that includes new primary objectives, major eligibility changes, and/or addition of a treatment arm
- Increase in overall sample size
  - affects the statistical plan and/or increases risk
- Addition of a study procedure that poses greater than minimal risk or substantially increases participant burden
- Significant change in primary objectives, including changes to study population of interest and/or changes to endpoints after study enrollment has begun
- Changes related to investigational drug or device such as:
  - Addition of a new drug in combination with the prior treatment plan
  - increase in dose and/or strength
  - frequency of administration
  - method of administration (e.g., oral to intravenous)
  - Addition of a new modality/device to the existing treatment plan
- Blood draws which exceed the Institutional Blood Volume Collection Guidelines (see Institutional Policy CLN0508) (adding PKs and PDs)
- Addition of tissue banking for future use
  - non-specified use or testing specimens in a non-CLIA environment for clinical decision-making
- Addition of genetic testing
- Addition of new treatment arm
- Change or addition of a major instrument that involves increased participant burden (e.g., addition of several questionnaires)
- Adding a vulnerable population (children, pregnant participants)

Informed Consent

- Addition of risk information where such risks alter the risk/benefit ratio including:
  - potential birth defects possibly linked to protocol participation
  - new safety information exists/long-term safety effects identified
- Increase in study burden for research participants including additional research-required/related procedures
- Addition of the requirement barrier method of birth control due to a new safety concern
- Substantial change in remuneration for participation that might be seen as coercive or inappropriate for the level of risk involved

Research Staff Changes

A change in research staff, including the roles of PI, Co-PI or Collaborator is a major revision if the newly identified individual is not qualified by education and training, as assessed by the IRB, does not have the required licensure or credentials to carry out the assigned research responsibilities or a significant new financial conflict of interest is being introduced.

EXPERT CONSULTANTS

For amendments that include extensive changes to the protocol design, new or revised non-validated survey/questionnaire/assessment tools, or complex regulatory issues (see Table 3), in addition to review by the convened IRB, the IRB may request that an expert consultant provide guidance related to the overall changes included in the amendment, or specific components of the changes. Expert consultation may include, but is not limited to, the following areas: 1) scientific review and validity (may utilize prior scientific reviewer, if available); 2) Biostatistics; 3) Legal and Compliance; 4) Pharmacy; 5) Behavioral Science; and 6) Clinical Ethics.

Investigators will be informed if the IRB has requested that their amendment requires review by an expert consultant. The reviews from these expert consultants will be provided to the convened IRB for consideration as part of the IRB review.

INVESTIGATOR RESPONSIBILITIES

Researchers should be mindful to submit changes to the IRB in a timely manner as soon as the change is received from the Sponsor, or Lead Site, to prevent delays in treatment. The IRB recommends that Sponsor amendments (any changes to the protocol) be submitted for review within 30 days after receipt from the Sponsor.

Evaluate Change to Determine Timeframe of Review: The researcher should reference the Regulations, and use the tables (e.g., Tables 1-3) above for guidance to evaluate whether a change may be reviewed by the IRB using the expedited review procedure or will require review by the convened IRB so as to allow appropriate time for the change to be reviewed and approved by the IRB prior to implementation.

Submit the Change to the IRB using PDOL (including the required material):

MD Anderson uses an on-line submission system called Protocol Document On-Line (PDOL) to submit new and amended protocols to our IRB. The following documents are part of the protocol package that remains in the system at all times:

- Protocol
- Signature Pages (PI, Co-PI, Collaborator)
- Appendices
- Informed Consent(s)
- Internally-required documents (Department Chair's Protocol Review and Prioritization and Abstract)

Not every document is affected with each submission. Only the documents indicated in a resubmission cover letter are reviewed and approved by the IRB. The documents are approved until the next submission is approved or until the annual continuing review is due, whichever comes first.

The IRB accepts redline (track change) versions for all protocol and consent documents except the Abstract. If a redline version is not available, all changes will need to be documented as old text/new text in the resubmission cover letter.

Include the following in the resubmission cover letter found in PDOL:

- Summary of changes
- Red-lined version of the amended protocol (this should be available for industry-sponsored protocols)
- Clean copy of the protocol
- Scientific rationale for all changes to all documents. If there is a change to the abstract and/or informed consent document, please include appropriate rationale. It is not appropriate to state that "the change is made to match protocol" or "per the Sponsor"
- For documents that do not have a tracked changes version, include old text (strikethrough deleted text)/new text (bold text that is new)
- Attach the informed consent document as tracked changes (if applicable). **As a reminder, striking out the entire old text and bolding the entire new text is not acceptable as this does not appropriately identify for the IRB the change that was made**
- Assessment from PI as to whether or not the revised Investigator's Brochure includes risk information that may require a change to the protocol or the informed consent document

For detailed instructions on how to submit changes, reference the PDOL User Guide (Section 11.2 - Resubmitting Your Protocol).

Administrative Letters from Sponsors

These are typically submitted as correspondence or memos from the Sponsor noting changes to the protocol when the Sponsor has not yet provided an amended protocol.

Administrative letters should be submitted in the following manner:

- Make changes to the Abstract and Informed Consent
- Attach the administrative letter to the Protocol Page in PDOL
- Create a resubmission cover letter documenting the addition of the administrative letter and changes made to the Abstract and Informed Consent

Wait for IRB approval of the Change: It is the researcher's responsibility to obtain IRB approval of changes to research prior to implementing the proposed modifications. Changes

that are required for immediate patient protection based on new safety concerns identified with the study drug and/or procedure may be implemented prior to IRB approval but IRB approval should be pursued and obtained immediately.

REASSIGNING HOME IRB

Revisions are required to be reviewed by the IRB of record (home IRB). In limited circumstances and with an appropriate justification, the researcher may request that a revision be reviewed by the non-home IRB. Both the home IRB Chairperson and the non-home IRB Chairperson must agree to the presentation of the revision at the non-home IRB. The researcher will be notified in writing of the reviewing IRB designation.

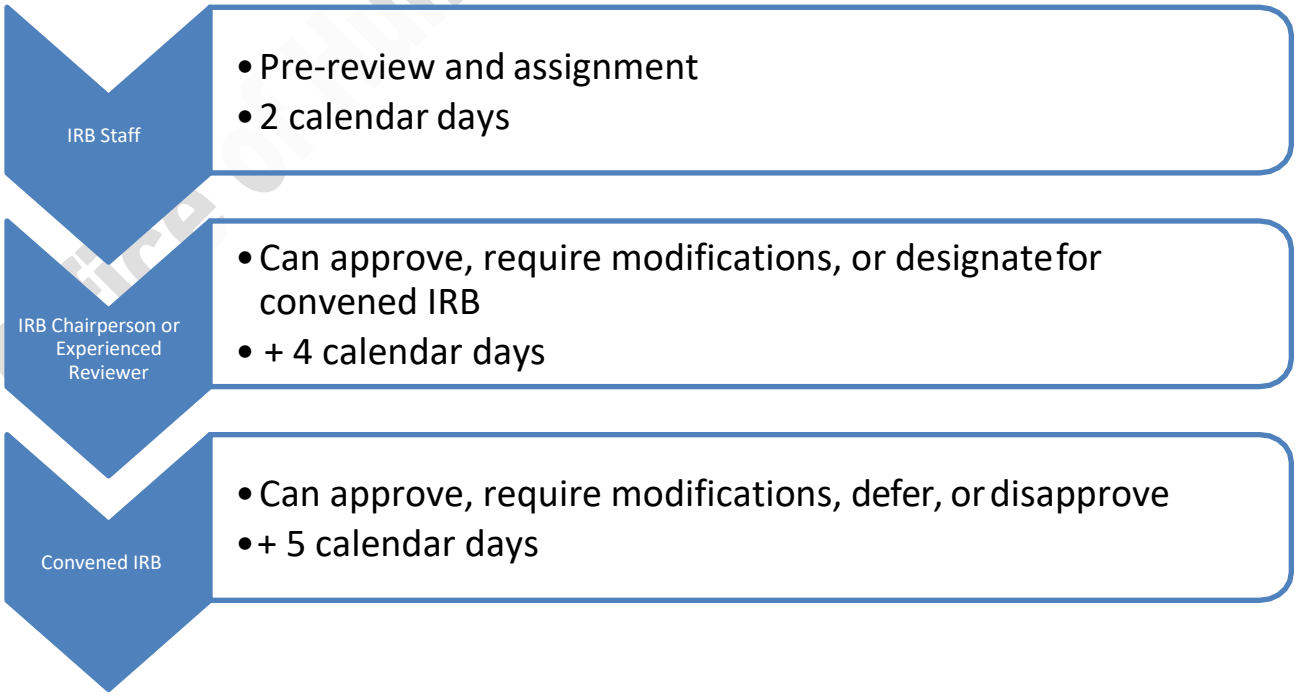
Some examples of appropriate justifications for IRB reassignment are: 1) there is a patient safety issue, and the amendment needs to be reviewed immediately by a convened board, 2) the home IRB will not meet for more than 2 weeks (happens with 5th weeks or during certain holidays); 3) an IRB Chair or member has a significant COI with the amendment being presented.

IRB REVIEW PROCEDURES FOR PROTOCOL CHANGES

IRB Pre-Review Process: IRB staff will conduct an initial pre-review for completeness and triage the change by sending to an experienced reviewer designated by the IRB Chairperson from among the members of the IRB ((21 CFR 56.110(b); 45 CFR 46.110(b)(2)).

The experienced reviewer will make an initial assessment of the appropriate level of IRB review required based on **Tables 1-3**. Figure 1 below shows the IRB responsibilities and turnaround times. These turnaround times may vary based on the IRB assessment of the submission.

Figure 1: IRB Reviewer Responsibilities and Turnaround Times



Review and Approval Criteria: The criteria for reviewing and approving changes to research are the same as those for initial review of a new protocol. Therefore, the IRB Chairperson or experienced reviewer, or a convened IRB must determine that all of the following requirements are satisfied as required per the federal regulations:

- Risks to subjects continue to be minimized and reasonable in relation to anticipated benefits;
- Selection of subjects continues to be equitable;
- Informed consent is sought or waived in accordance with 45 CFR 46.116 as well as 21 CFR 50.25 for FDA-regulated research;
- Informed consent will be documented or documentation waived in accordance with 45 CFR 46.117 and 21 CFR 50.27 for FDA-regulated research;
- The research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects, when appropriate;
- There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, when appropriate;
- Appropriate safeguards for vulnerable subjects are provided; and
- If multi-site research, the study management of information relevant to protection of subjects is adequate

Review of Recruitment, Screening and Consent Documents: When reviewing the recruitment, screening and/or informed consent documents, the IRB will ensure the following:

- The currently approved or proposed documents are complete, accurately reflect the information in the study application, and meet all the federal regulatory requirements and applicable IRB approval; and
- Any new findings that may relate to the subject's willingness to continue participation are provided to the subject in an updated informed consent form or addendum to the informed consent form.

Please see the HRPP Manual and the IRB Policy on Advertising and Recruiting for a Research Study for additional requirements.

Period of Approval for Changes to Research: The approval period does not change following IRB approval of changes to research.

INSTITUTIONAL REQUIREMENTS

Once IRB approval is granted for the changes to the research, there are additional institutional requirements that must be met in order to ensure that the changes align with financial and clinical operations. The IRB approval memo will be issued once these requirements have been verified by the IRB staff. When applicable, these requirements include:

- Coverage determination and budget review
- Clinical Content Template review
- Protocol Fact Sheet
- Investigational Pharmacy review

- Institutional Biorepository Utilization Committee (IBUC) approval (for protocols that are utilizing or establishing a tissue repository)

REFERENCES

45 CFR §46.109 (a) and (d)
45 CFR §46.110(a)(b)(c)(d)
21 CFR §56.109 (a) and (e)
21 CFR §56.110 (a)(b)(c)(d)
OHRP Expedited Review Categories (1998)
(https://www.hhs.gov/ohrp/regulations-and- policy/guidance/categories-of-research-expedited-review-procedure-1998/index.html)

Date	Action	Initials	Description
07/25/2018	AWC	WAQ	IRB3 reviewed and approved policy with minor change to clarify the types of research staff changes that are considered major and would require review by the convened board.
12/13/2018	NAI	WAQ	Revised to change description of change in research staff and increased patient burden.
06/06/2019	Update	YC	Added the addition of site
1/8/2020	Update	JH	Fixed graphic, formatting, and page numbering