AAH RSPP GUIDANCE
IRB Decisions

PURPOSE
This guidance outlines the IRB decisions allowable by the regulations under 45 CFR 46.109(a) when conducting an initial or continuing review of a nonexempt research study, or a review of proposed changes to a previously approved nonexempt research study.

It should be noted that the regulatory criteria for approval (45 CFR 46.111) are the same for studies reviewed by the convened IRB or via an expedited review process.

Definitions of Italicized words can be found in the AAH RSPP Glossary.

GUIDANCE
Under the regulations, what are allowable decisions of the IRB in reviewing non-exempt human subject research?
Under HHS regulations at 45 CFR 46.109(a), an IRB can take any of the following actions in reviewing non-exempt human subject research:

Approval: The protocol and accompanying documents may be approved as submitted.

Deferred: When the convened IRB has significant questions or requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the regulatory criteria for approval, IRB approval of the proposed research is deferred pending subsequent review by convened IRB of responsive material.

Conditional Approval: The protocol and accompanying documents may be approved with conditions issued by the IRB. The IRB may approve research with conditions if, given the scope and nature of the conditions, the IRB is able, based on the assumption that the conditions are satisfied, to make determinations that all of the regulatory criteria for approval are met. When the IRB approves research with conditions, verification procedures must be included as part of the IRB approval process.

Disapproval: The protocol and accompanying documents fail to meet one or more regulatory criteria of approval. Note that a disapproval decision may not be made as part of expedited review.

NOTE that the IRB’s review of a research study may be Tabled should the IRB lose quorum or meeting time expires before an IRB action can occur. The IRB Action of Tabling is not directly related to the Criteria for Approval decision.
When can research be ‘approved’?
HHS regulations at 45 CFR 46.102(h) define IRB approval as the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

In order to approve research, IRBs must determine that all of the requirements at 45 CFR 46.111 (regulatory criteria of approval) are satisfied.

Can the IRB add additional protections to a study that is deemed approvable?
Yes, the IRB has the option of requiring more frequent review than annual OR verification from external sources that no material changes have been made to the research.

What protocols may require more often than annual review?
Determination of which studies require review more often than annually is done at the time of protocol review, on a case by case basis, depending upon protocol specific factors.

Studies may be reviewed by the IRB more frequently if the study is high risk, if the IRB feels that the study population is especially vulnerable, if previous similar studies indicate a high incidence of unanticipated problems or noncompliance, or if the IRB feels that close monitoring is indicated. The IRB may request interim reports at intervals deemed appropriate by the IRB in addition to the required continuing review.

A determination of more often than annual review will be documented in the minutes.

What protocols may require verification from other sources?
Determination of which studies need verification from sources other than the investigators that no material changes have occurred since previous IRB review is done on a case by case basis either by the primary reviewer at initial review, continuing review, or through information received (e.g., adverse event or unanticipated problems to subjects or others reports or complaints) and would depend upon protocol specific factors.

The need to verify any information will be determined by the convened IRB and documented in the meeting minutes. The purpose of the verification will be to provide necessary additional protections to subjects when deemed appropriate by the IRB.

Third-party verification may be required for studies such as the following:

- Studies that involve a potential high risk to subjects;
- Studies that involve vulnerable populations;
- Studies that involve large numbers of subjects;
- Studies conducted by an investigator who has had incidences of Serious or Continuing noncompliance;
- The information provided by the investigator is inconsistent with other information known to the IRB and the inconsistency cannot be resolved through communication with the
investigator;

- The IRB has concerns about the accuracy or integrity of the information submitted or has reason to believe the investigator/study staff has submitted inaccurate information;
- The IRB has concerns about the manner in which the study will be or is being conducted;
- Any other reason where the IRB believes verification should be required.

Projects that have been determined to need third-party verification will have such verification performed by the Research Compliance Analyst, RSPP Director, IRB Chair, or other IRB member. Results of the verification will be reported to the IRB as necessary.

**What are conditions of approval [‘conditional approval’]?**

In the course of initial or continuing review of research, or review of proposed changes to previously approved research, IRBs often request that investigators make specified changes to the research protocols or informed consent documents; or submit clarifications or additional documents. This is based on the assumption that when the conditions are satisfied, the IRB is able to make all of the determinations required for approval at 45 CFR 46.111.

The IRB may require the following as conditions of approval of research:

1. Confirmation of specific assumptions or understandings on the part of the IRB regarding how the research will be conducted (e.g., confirmation that the research excludes children);
2. Submission of additional documentation (e.g., certificate of ethics training);
3. Precise language changes to protocol or informed consent documents; or
4. Substantive changes to protocol or informed consent documents along with clearly stated parameters that the changes must satisfy.

More information on conditional approval can be found in the OHRP guidance: Approval of Research with Conditions (2010).

**Verification process.** When the IRB approves research with conditions, verification procedures must be included as part of the IRB approval process. The IRB must designate an individual (e.g. the IRB chairperson and/or other individual(s) with appropriate expertise or qualifications) to review responsive materials from the investigator that are required by the IRB, and determine whether the conditions of approval have been satisfied (45 CFR 46.102(h)). This verification process is not considered to represent the review and approval of minor changes under an expedited review procedure. Documentation of the verification process will be kept with the study file.

**How is the PI made aware of conditions of approval?**

The Research Compliance Analyst in the RSPP office will provide the PI with a written description of all conditions of approval that must be satisfied in order to secure IRB approval. If the conditions of approval include specific changes made by the IRB to the consent
document/protocol/submission application, the PI must acknowledge and authorize these changes. This documentation will be retained in the study file.

If the PI chooses not to agree with the conditions of IRB approval, the study will be brought back to the Full IRB for review. The PI should provide justification for not addressing the condition as outlined by the IRB.

When conditions of approval have been issued by the IRB, responsive material should be provided to the RSPP within 90 days of the IRB meeting. However, this period may be extended if the PI communicates a need for an extension. If there is no communication by the PI within the 90 days period, the RSPP office may withdraw the study. The PI will be notified of this action in writing.

How do conditions on IRB approval at the time of initial review affect the initiation of the research?

Whenever the IRB approves a research study with one or more conditions at the time of initial review, the effective date of the initial approval is the date on which the IRB chairperson (or any other individual(s) designated by the IRB) has reviewed and accepted as satisfactory any revised protocol or informed consent documents or any other responsive materials required by the IRB from the investigator. This effective date is documented in the IRB approval letter. See RSPP Guidance: IRB Approval Dates and Expiration of IRB Approval.

No research study activities involving human subjects may be initiated until the conditions have been satisfied and the approval becomes effective.

What happens if the reviewer designated by the IRB does not find that the responsive materials satisfy the conditions of approval?

If the designated reviewer(s) determines that the responsive materials do not satisfy the conditions of approval stipulated by the IRB, then the IRB approval has not become effective, and the investigator may not proceed with the research. The research study must be brought back to the convened IRB.

Can changes – besides conditions of approval – be made to the research study prior to issuance of IRB approval?

It is the position of the AAH RSPP/IRB to not allow additional changes to the research proposed by the investigator until all conditions of approval have been satisfied and the protocol documents finalized. Such additional changes would be required to be submitted as Changes in Approved Research (see RSPP SOP #9).

The only exceptions to this requirement are:

- Protocol corrections that are only administrative in nature (e.g., correction of typographical and spelling errors in the protocol). These administrative changes may be made as part of the IRB approval process and would not require submission of a
Change as these corrections are not considered to be changes to the research.

Must the IRB records include documentation of conditional approval and verification that conditions are satisfactorily met?
When the IRB approves research with conditions, the IRB must document the conditions, both to the investigator and in the IRB minutes for research reviewed at a convened meeting, or elsewhere in the IRB records for research reviewed under an expedited review procedure, as indicated in 45 CFR 46.115(a).

All correspondence between the IRB and the investigator regarding the conditions of approval set forth by the IRB must be maintained in the IRB records.

When must research be disapproved or deferred?
Any time the IRB reviewing a research project cannot make one or more of the determinations required for approval (45 CFR 46.111), the IRB must not approve the research project. This applies to both initial and continuing review of research, and review of proposed changes to previously approved research.

The IRB can either disapprove the project, or defer it’s review to a future convened board meeting. When deferring the review of a study, the IRB may require that the investigator:
- make changes to the protocol or informed consent documents, OR
- submit clarifications or additional documents prior to the next review.

If the IRB defers a research study, the research may not proceed until the IRB reviews the revised research project and approves it at a subsequent convened meeting.

Is there an appeal process for the PI?
A PI may appeal the IRB’s revisions required to satisfy the regulatory criteria for approval ("conditions of approval") This appeal must be in writing reviewed/considered by the convened IRB at a later meeting.

A PI may also appeal an Aurora IRB decision to disapprove a study. Any such appeal must be in writing and must be reviewed by the IRB at a convened meeting. The PI may appear before the IRB at the meeting. If the appeal is denied and the study disapproval upheld, the IRB’s decision cannot be overturned.

Can the institution approve a research study that has been disapproved by the IRB?
Neither the Institutional Official nor any AAH Administrator shall have the authority to approve the conduct of a research study or use of an investigational drug or investigational device at an AAH facility when the IRB has not approved the research study. [See System policy 2467]

The Institutional Official, in consultation with an IRB Chair or AAH Administrator(s) may disapprove or impose additional conditions on the conduct of a research study that has received IRB approval.
What does it mean when I receive a ‘statement of acknowledgment’ from the RSPP?
A statement of acknowledgment notes that the RSPP has received and reviewed the submitted information, and in most cases, no further action by the IRB is necessary. If further consideration by the IRB is taken, the PI will be made aware of the action in written communication.

REQUIREMENTS
- Common Rule Regulations: 45 CFR 46.102; 45 CFR 46.109; 45 CFR 46.111; 45 CFR 46.115
- FDA Regulations 21 CFR 56.111
- OHRP Guidance: Approval of Research with Conditions (2010)
- AAHRPP Accreditation Standards/Elements: II.2.E, F
- RSPP SOPs: 9 and 10
- RSPP Guidance: IRB Approval Dates and Expiration of IRB Approval, Expedited Review
- System policy 2467