UC Davis Institutional Review Board

Approval with Conditions

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Objectives

- Define what IRB Approval with Conditions means.
- Understand the circumstances that preclude the IRB from approving research with conditions.
- Understand the circumstances that permit the IRB to approve research with modifications.

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Criteria for Approval

- ✓ Risks are minimized
- ✓ Risks are reasonable in relation to anticipated benefits
- ✓ Selection of subjects is equitable
- ✓ Informed consent will be sought and documented appropriately
- ✓ Data will be monitored to ensure subject safety and compliance
- ✓ There are adequate protections for subject privacy and data confidentiality
- ✓ There are additional safeguards for vulnerable populations
  (children, pregnant women, prisoners)

References: 45 CFR 46.111; HRP – 314 Criteria for Approval

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What does Approval with Conditions mean per the Regulations?

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What does IRB *Approval with Conditions* mean?

The IRB often requests that Investigators make **specified** changes to the research protocols or consent form documents. Here, at UC Davis, we refer to this as

"Approved with Modifications,
Modifications Required,
or Directive Modifications"

the OHRP Guidance refers to it as

Approval of Research with Conditions

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What does IRB *Approval with Conditions* mean?

"IRB approval with conditions (sometimes referred to as "conditional approval" or "contingent approval") means that at the time when the IRB reviews and approves a submission, the IRB requires as a condition of approval that the investigator:

(a) make **specified** changes to the research protocol or informed consent document(s),
(b) **confirm** specific assumptions or understandings on the part of the IRB regarding how the research will be conducted, or
(c) submit additional documents, such that, based on the assumption that the conditions are satisfied, the IRB is able to make all of the determinations required for approval under the HHS regulations at 45 CFR 46.111 and, if applicable, subparts B, C, or D of 45 CFR part 46.

With respect to research reviewed and approved with conditions by the IRB at a convened meeting, note that because the IRB is able to make all these determinations, the IRB **may designate the IRB chairperson (and/or other individual(s) with appropriate expertise or qualifications)** to **review** responsive materials from the investigator and determine that the conditions have been satisfied, and further review by the IRB at a **subsequent convened meeting would not be necessary."**

References: Approval of Research with Conditions: OHRP Guidance (2010) | HHS.gov

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What circumstances preclude the IRB from approving research?

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What circumstances preclude the IRB from approving research?

"Any time the IRB reviewing a research project cannot make one or more of the determinations required for approval by the HHS regulations at 45 CFR 46.111 and, if applicable, subparts B, C, or D of 45 CFR part 46, 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.

For example, the IRB must not approve a proposed research project undergoing initial review when the IRB (a) is unable to make the required determinations about research risks and benefits, the adequacy of privacy and confidentiality protections, or the adequacy of the informed consent process because the research protocol provides insufficient information related to these aspects of the research, and (b) is **unable to specify changes** to the research protocol that if made would allow the IRB to make these required determinations."

References: Approval of Research with Conditions: OHRP Guidance (2010) | HHS.gov

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OHRP Examples of Reasons to Defer or Disapprove Research

1. Providing a justification for using a placebo and withholding currently available treatment for a serious medical condition for subjects assigned to a control group (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(1) and (2));

2. Providing a justification for enrolling children in the research and an explanation of how the research would satisfy the requirements of subpart D of 45 CFR part 46 (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under subpart D of 45 CFR part 46);

3. Revising the study hypothesis and, accordingly, the study design (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111 (a)(1), (2), and (4));

4. Providing a description of procedures that the control group will undergo (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(1), (2), and (4));

References: Approval of Research with Conditions: OHRP Guidance (2010) | HHS.gov

OHRP Examples of Reasons to Defer or Disapprove Research (cont.)

5. Providing clarifying information needed to assess the risks to subjects, such as clarifying whether individuals who have taken aspirin within 14 days prior to enrollment will be excluded from the study because of concerns about the risks of bleeding (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(1) and (2);

6. Clarifying the timing and circumstances under which the informed consent of prospective subjects will be sought (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(4);

7. Providing a plan to implement additional subject monitoring in order to reduce risks to subjects, given the number of serious adverse events that have occurred in study subjects since the prior IRB review (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(1), (2), and (4)).

References: Approval of Research with Conditions: OHRP Guidance (2010) | HHS.gov

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What circumstances permit the IRB to approve research with modifications?

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What circumstances permit the IRB to approve research with modifications?

"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 all of the determinations required for approval under the HHS regulations at 45 CFR 46.111 and, if applicable, subparts B, C, or D of 45 CFR part 46. The authority to approve research with conditions extends to the IRB's initial review of research, continuing review of research, and review of proposed changes to previously approved research. This authority also applies to IRB review of research at a convened meeting or under an expedited review procedure."

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.

References: Approval of Research with Conditions: OHRP Guidance (2010) | HHS.gov

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OHRP Examples of Approved Research with Conditions (Modifications)

1. Requiring submission of an endorsement letter from a department chair, as required by institutional policy, and designating an IRB staff member to confirm receipt of the required documentation;

2. Requiring correction of minor grammatical and typographical errors in the informed consent document, and designating an IRB staff member to review the revised consent document and confirm the required corrections were made;

3. Requiring a listed investigator provide a copy of his approved clinical privileges/hospital staff appointment document in order to confirm he has approval to perform the procedures (e.g., percutaneous liver biopsies) proposed in the research protocol at the institution where the research is to be conducted, and designating an staff member to review this document and confirm that the clinical privileges of the listed investigator include authorization to perform such procedures.

References: Approval of Research with Conditions: OHRP Guidance (2010) | HHS.gov

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OHRP Examples of Approved Research with Conditions (Modifications)

4. Requiring that the investigator re-locate in the informed consent document the statement "You will receive $500 for participating in this study" from the "Benefits" section to a separate section, "Compensation," and designating an IRB staff member to review the revised informed consent document and verify the re-location;

5. Requiring the investigator – in order to ensure that risks to subjects are minimized – add "a history of aspirin use in the past 14 days" to the exclusion criteria for subject enrollment in the research protocol, and designating an IRB staff member to review the revised protocol and verify that the stipulated language was added to the exclusion criteria;

6. For a randomized clinical trial comparing two types of surgical procedures, requiring the investigator – in order to ensure that informed consent will be obtained under circumstances that provide prospective subjects with sufficient opportunity to consider whether or not to participate – revise the protocol to indicate that informed consent of the prospective subjects will be sought by the investigator during an outpatient clinic visit at least one week before the surgery, and designating an IRB staff member to review the revised protocol and verify that the requested language regarding the process for soliciting informed consent from subjects was added to the protocol.

References: Approval of Research with Conditions: OHRP Guidance (2010) | HHS.gov

OHRP Examples of Approved Research with Conditions (Modifications)

7. Requiring the investigator to (a) confirm that any standard contrast material used in radiological procedures dictated by the research protocol will be limited to agents and dose levels specified in precise detail by the IRB, and (b) submit a revised protocol which includes the precise agents and dose levels, and designating an IRB staff member to review the revised protocol and verify that the changes made by the investigator match those specified by the IRB;

8. Requiring that the investigator modify the informed consent document to include standard template language used for research involving college psychology students, stating that comparable non-research alternatives for earning extra credit will be offered to students who choose not to participate in the research, and designating an IRB staff member to review the revised informed consent document and verify the addition;

9. Requiring the addition to the consent document of a description of the risks of a standard chemotherapy drug, where the risks are well-described in the research protocol, and designating an IRB member or consultant who is knowledgeable about those risks to review the revised consent document and confirm that the description of the risks is satisfactory.

References: Approval of Research with Conditions: OHRP Guidance (2010) | HHS.gov

OHRP Examples of Approved Research with Conditions (Modifications)

10. Requiring revision of the research protocol to include a description of the type and amount of standard contrast material to be used in the radiological procedures dictated by the research protocol, and designating an IRB member or consultant who is a radiologist to review the revised protocol and ensure that the use of standard contrast material is medically appropriate;

11. Requiring simplification of the description of the study risks in the consent document to be at an 8th grade comprehension level, and designating the IRB chairperson to review the revised consent document and ensure that risks are accurately described and understandable at an 8th grade comprehension level;

12. Requiring the research protocol be revised to include a plan for (a) informing subjects about the results of standard clinical tests performed as part of the research (e.g., cardiac function tests), and (b) referring subjects for appropriate clinical follow-up, and designating an IRB member or a consultant with appropriate clinical expertise (e.g., a cardiologist) to review the revised protocol and confirm that the plan is medically appropriate.

References: Approval of Research with Conditions: OHRP Guidance (2010) | HHS.gov

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Directive Modifications or Deferral?

Let's look at some examples

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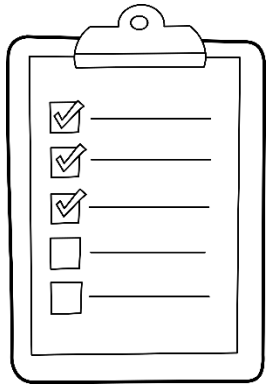
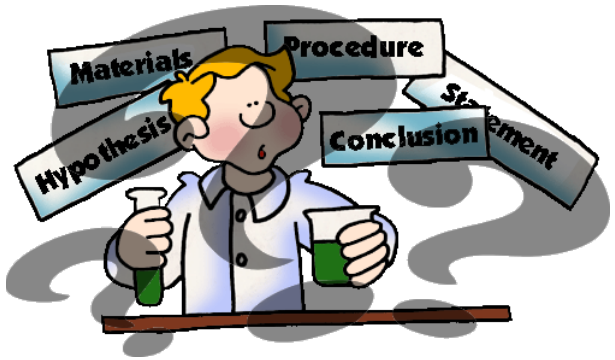
Making Comments:



Directive comments that are itemized and offer instructions that can be verified by a Committee Analyst, IRB Chair, or a designated Reviewer in a response—such as a specific change of language marked by page, paragraph, and sentence—can contribute to a determination of Modifications Required.



Comments that require clarifications or changes that are conceptual, invite researcher interpretation of information, relate to the tone or context of subject-facing materials, or will require discretion by reviewers to determine if a response is satisfactory cause a Deferral.

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Directive Modifications or Deferral?

This is community-based participatory research. The committee is concerned about the risk of stigmatization of the Hmong community. In the Initial Review Application, please provide a description of what has been done in consultation with the Hmong community leaders that will guide this research.

Directive Modifications Or Deferral?

Deferral

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Directive Modifications or Deferral?

Protocol, Consent and Email Advertisement: The protocol states there are no known risks to pregnant women. Clarify why pregnant women are excluded, or will be removed if they become pregnant. Please provide additional information regarding the fetus. The consent form states that the risks to the fetus are unknown. Are there risks to the fetus?

Directive Modifications Or Deferral?

Deferral

Directive Modifications or Deferral?

Protocol and Consent: Foods are sources of pre and probiotics. For example, yogurt and kefir with live cultures are considered a probiotic; dairy free fermented beverages like Yakult or other fruit-based kefirs are probiotics. Prebiotics in food products are very widespread; most notably inulin is added to many energy bars and snack bars – will these be limited?
Create a list of pre- and probiotics that need to be avoided during the study.

Directive Modifications Or Deferral?

Deferral

Directive Modifications or Deferral?

Consent, Online: Remove the section for the ClinicalTrials.gov language for clinical research as it's not applicable here.

Directive Modifications Or Deferral?

Directive Modifications

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Directive Modifications or Deferral?

Consent Form, Page 2, What Happens If I Say Yes, Before Paragraph 1, Add the following: *Before the child begins the study, parents will view the images to determine if the images that may provoke certain feelings are appropriate for their child.*

Directive Modifications Or Deferral?

Directive Modifications

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Directive Modifications or Deferral?

Advertisement, Email, Exclusion Criteria, Second Bullet: Add "compromised immune system" so it says

Subjects must have no history of diabetes, known cardiovascular disease, compromised immune system, malignancy, kidney disease, or chronic steroid use.

Directive Modifications Or Deferral?

Directive Modifications

Main IRB Determinations

Determination	Meaning
Approval 	Ethical criteria are satisfied. Research can begin when all other institutional approvals are obtained.
Approval with Administrative Comment 	Ethical criteria are satisfied. Research can begin when all other institutional approvals are obtained. The IRB provides an administrative comment about some aspect of the project or its conduct outside of the criteria for approval.
Approval with Modifications Required 	The IRB requires modifications in order to approve the research. Research cannot commence until a final approval is received.
Deferral 	The IRB cannot approve the research as submitted and describes reasons or modifications that might make the research approvable; the IRB requests additional information from the researcher. Reviewer comments use words like: clarify, provide more information, define, simplify, interpret.
Disapproval 	The IRB cannot approve the research as submitted and cannot describe modifications that might make the research approvable.

Committee Member Resources:

- https://research.ucdavis.edu/policiescompliance/irb-admin/members/
- Secondary Reviewer Summary Templates (New, Modification, and Continuing Review)
- Reviewer Placemat

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Reviewer Placemat

Devices
21 CFR 812

- **Significant Risk (SR)**

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

- **Non-Significant Risk (NSR) Abbreviated IDE (Checklist 418 Required)**
- **IDE exempt (no Checklist required)**

Determinations
Approval
Approval with Minor Modifications
Deferred
Disapproval

RNI Determinations
Non-Compliance: Failure to comply with the requirements of an applicable law, regulation, or institutional policy pertaining to the protection of human subjects, and/or with the requirements or determinations of an IRB.

Continuing Non-Compliance: A pattern of noncompliance that indicates an inability or unwillingness to comply with the requirements of an applicable law, regulation, or institutional policy pertaining to the protection of human subjects and/or with the requirements or determinations of an IRB.

Serious Non-Compliance: Noncompliance that adversely affects the rights or welfare of participants. Note special standard for DoD funded research.

Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO) – Indicates subjects or others are at an increased risk (Serious, Unexpected, Probably Related)

None of the Above (Acknowledge)

Is an IND Required?

- Is drug FDA approved? If "No"– IND required
- If "yes" Is the drug used off label? If no – No IND
- If "yes" Does the investigation involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

Studies with/of Supplements

- Supplement breakdown
- Where is the supplement coming from: Company or OTC
- Statement of Ingredients
- Check inclusion/exclusion criteria & ICF for Food Allergies or considerations
- Composition and microbial analysis report
- Is an IND required?
- Following Current Good Manufacturing Practices (cGMP) for dietary supplements being followed

Waiver of Documentation of Consent

- Minimal risk
- No procedures that usually require consent

Or

- Not under FDA.
- Principle risk is breach of confidentiality.
- Only record linking subject to research would be the consent document

Criteria for Approval
45 CFR 46.111 and 21 CFR 56.111

1. Risks to subjects are minimized by (1) using procedures, consistent with sound research design; using procedures already being done on the subjects for other purposes; and (2) without exposing subjects to unnecessary risk. Ask: Is there any way to minimize risk?
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
3. Selection of subjects is equitable.
4. Additional safeguards have been included in the study to protect the rights and welfare of subjects who are vulnerable to coercion or undue influence.
5. The research plan has adequate provision for monitoring the data collected to ensure subject safety.
6. There are adequate provisions to protect the privacy of subjects.
7. There are adequate provisions to maintain the confidentiality of data.
8. The informed consent process is adequate.
9. The documentation of informed consent is adequate.

Definition of Minimal Risk
The probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Conflicts of Interest as a Reviewer
The following would fall under financial conflicts of interest as a Reviewer (including subsidiaries and parent companies):

Consultant/Speaker bureau
Advisory board membership
Honorarium recipient
Stockholder
Editorial board involvement
1571/1572 investigator/collaborator

Investigator Conflict of Interest Management Plans

- Disclosure
- Conflicted party cannot obtain consent
- Conflicted party cannot recruit
- Conflicted party cannot analyze data
- Conflicted party cannot be associated with the research

CAPA
What was the error?

Who was responsible, and how does PI responsibility relate?

How did the error occur?

Why did the error occur?
(ask how and why five times!)

What are the corrective actions?
- Disclosure
- Reconsent
- Redoing procedures
- Excluding data

What are the preventive actions?
- Checklists
- Independent Monitoring
- Subject specific documentation

Is new training needed?

Is re-evaluation needed within a timeframe (6-9 months)

Document Everything

Criteria for Minors
Subpart D Categories
45 CFR 46

404 – Level 1
- Minimal Risk
- Benefit or no direct benefit
- 1 Parent Signature

405 – Level 2
- Greater than minimal risk
- Risk is justified by anticipated benefit
- Risk/benefit at least as favorable as alternative approaches
- 1 or 2 Parent Signatures

406 – Level 3
- Minor increase over minimal risk
- Commensurate
- Likely to yield generalizable knowledge of vital importance
- 2 Parent Signatures

407 – Level 4
DHHS Review and approval required

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THANK YOU!

The efficient review and approval of research is a gift to the discovery and dissemination of knowledge.

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