Human Research Ethics Training Tips: Conflict of Interest

What is a COI at UNC?

Conflict of interest is a situation in which **financial or other personal** considerations:

- may compromise,
- may involve the potential for compromising, or
- may have the appearance of compromising a Covered Individual's objectivity in meeting University duties or responsibilities, including research activities. *UNC Board of Governors Policy Manual*

The bias that such conflicts may impart can affect many University duties, including:

- decisions about personnel,
- the purchase of equipment and other supplies,
- the collection, analysis and interpretation of data,
- the sharing of research results,
- the choice of research protocols,
- the use of statistical methods,
- and the mentoring and judgment of student work.

Researcher COI: OHRE SOP 701

2.4.7 Investigator Conflicts of Interest (COI)

- The IRB research application asks specific questions regarding the investigator and research team compliance with disclosure requirements and whether or not any COI management plans are in place. As part of its review process, the IRB will make a final determination as to whether any conflict of interest is adequately addressed and protects the human subjects in the research. **The IRB has final authority** to determine whether the declared COI and the management plan, if any, allow the study to be approved.

When Are COI Disclosures Required?

- Per OHRE determination:
  - Initial
  - Annual Renewal
  - Modifications
    - For any new person switched into the PI role
    - For any new personnel added if role requires
    - For all required personnel if new funding source added

Role Based Standards – IRB Studies

- Principal Investigator
  - <$10K Consulting, per company, per calendar year
  - Generally cannot be assessing own IP*
  - Generally cannot have equity*
  - Additional checks and balances to mitigate COI, meet compelling circumstances
- Note there are a few studies with exceptions to PI standards for pilot or non-treatment studies; case by case review. Included in COI finalization letter.

- Co-Investigator
  - $$ of consulting affects study duties
  - $$ or % of equity affect study duties, particularly when combined with other interests. Must meet compelling circumstances.
  - Very strong concerns about assessing own IP, particularly in treatment study (potentially not allowable). Must demonstrate compelling circumstances. Limitations on study activities are usually determined.
  - PI copied on final determination
- Other Roles
  - Disclosure
  - Potential firewall or change in activities
  - PI copied on final determination

OHRE Office / IRB Meetings

- **Specific Points of Concern**
  - Review and/or Manage
  - Study Design
  - Obtaining Informed Consent
    - Referring Patients
    - Influence
  - Adverse Event decisions
  - Research specific decisions versus clinical care
  - Access to research information
  - Data Analysis involvement
  - or non-participation in human study

Expedited Review

- IRB Analyst reviews
- IRB Chair confirms management

- **Full Board Review**
  - IRB Analyst
  - IRB Chair
  - IRB Committee Assigned Reviewers
  - Document in Minutes: confirmation, additional requirement

Hard stop in IRBIS System that IRB Approval cannot proceed until COI review is completed

IRB Member COI

1. IRB Members are responsible for making known any potential or perceived conflict of interest (COI) concerning protocols reviewed by the IRB. Examples of conflict of interest include:
   a. Participation in the conduct of the study (PI, co-PI, study coordinator, or other key personnel; receiving funding from the grant)
   b. Participation in the conduct of a competing study
   c. Supervisory role over the principal investigator of the research
   d. Stock, equity, or other financial interest greater than $10,000. Equity in a privately held company is considered a conflict, no matter the value.
   e. Compensation related to the research (i.e., consulting, speaking, advisory board)
   f. Patent, licensing agreement, trademark, copyright or other proprietary interest
   g. Corporate Board of Directors or executive relationship
   h. Participation in the study as a research subject
   i. Any other reason for which the member believes that he/she cannot provide an independent review.
   j. Participation of a spouse/significant other in the conduct of the study

2. IRB Members must declare any conflicts of interest at the meeting.
    a. The Chair will ask members to declare any COI at the beginning of the meeting. Members with COI must leave the meeting room for presentation and vote, unless asked by the IRB to remain briefly to answer questions or provide expertise.
    b. The COI declaration must be recorded in the minutes.

Office of Human Research Ethics Training Tips: Deferral of Studies

"OPRR recommends the following guidelines in such cases:

(i) ***When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must be deferred, pending subsequent review of responsive materials by the convened IRB.***

(ii) ***Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB chair or designated reviewer subsequently approve the research on behalf of the IRB."***

THE *'-ATION''* LIST

A protocol may be deferred if any of the following are required during review by a convened IRB:

Elabor*ation*

Clarific*ation*

Document*ation*

Explan*ation*

Justific*ation*

Modific*ation*

Adapted from Joseph F. Farmer, MD

If the question/stip are:

- **open ended,**
- **does not allow IRB to answer every 111 criteria,**
- **does not provide exact wording to be substituted in the consent, survey, ad, etc.; then MUST defer**

THE GRID

COI/Training for IRB NO: 16-1522

Full Name	Role	Department Name	IRB Training	COI WebID	COI Number	Initial COI Disclcosure	Potential Conflict	COI Review Process	COI Review Result
University of North Carolina at Chapel Hill (UNC-CH)									
David Wohl	Co-investigator	Medicine-Infectious Diseases	✓	214931	17-26586	✓	Yes	Completed	Admin Considerations
Cheryl Hendrickson	Regulatory Associate	Medicine-Infectious Diseases	✓		n/a	n/a			n/a
William Fischer	Principal Investigator	Medicine-Pulmonary	✓	214932	17-26587	✓		Completed	No Conflict
Tania Caravella	Regulatory Associate	Institute for Global Health and Infectious Diseases	✓		n/a	n/a			n/a

Review Process

- Unsubmitted
- Potential COI
- Pending
- Staff Review
- Chair Review (Designated)
- Committee Review
- Awaiting Submitter Response
- Awaiting Submitter Change
- Completed

- Acknowledgement
- **Transparency**
- **Admin Considerations**
- **FCOI Management**
- **Not Manageable**
- **Deferral**
- Rely Upon External
- **Rely Upon External (Manage)**
- Withdrawn
- Not Evaluated

From OHRP FAQs:

Examples of required changes or clarifications that generally would preclude the IRB from approving the research include the following:

1. **OHRP:** 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));

   Guidance:
   - How can the IRB evaluate the Risk:Benefit ratio without knowing this information?
   - Would withholding standard of care &/or medications currently on from the subject affect the subject's risk level?
   - Is the study design valid?
   - Will or could subjects be harmed by participation in this study?
   - Example: subject at Butner taken off meds, not hospitalized, hallucinated and killed someone.

2. **OHRP:** 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);

   Guidance:
   Children are a vulnerable population and require additional protections. The IRB needs to vote on & document which level of risk the study falls into and how many parents need to sign the consent to allow the child in the study.
   - Risk to the child from this study is…….
   - How is the study minimizing the risk……
   - How many parent(s) signatures are needed
   - How is assent obtained from the child
   - Know that "NO" from the child means "NO" unless the research holds out the only prospect of help for their condition.

   - **§46.404 Research *not involving greater than minimal risk.***

   - HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

   §46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

   - HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:
     - (a) ***The risk is justified by the anticipated benefit*** to the subjects;
     - (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
     - (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

- **§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.**

- **§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.**

3. **OHRP:** 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));

Guidance

- See #1.

- **IRB Minutes:** It is noted that the following text appears in the consent document: "Optional Sample for DNA will be collected on Day 1 to study the genes that can be potentially involved in the response to study drug. You will sign a separate consent form to do this optional study." In light of this, please address the following, as appropriate:

  - **Comment**:–Delete this question to the PI and tell subjects which you believe is the best design to minimize risk to subjects. ~~Are these optional 2 teaspoons of blood (10 ml) included in the 46 ml stated in A.4.2? If not, they should.~~
  - Be bold, direct the PI to do what you feel will best protect subjects.
  - If they disagree, then they can respond why they feel the IRB has misinterpreted the study.
  - Again, try to resolve these issues prior to the board meeting with an email to the research coordinator &/or PI.

- **IRB Minutes:** "Please add to the ICF that 2 teaspoons of patient blood may be collected and stored for additional studies."
  - **Comment:** Delete the language cited earlier in favor of this consent change.
  - **I**f the subject decides to join the optional study, then they know exactly how much more blood will be drawn and there will be no question about how much blood will be drawn for the main study.
  - The IRB can also properly assess the blood volume for this study (Is it within acceptable limits) and decide on risk.

4. **OHRP:** 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));

- **Comment:** This example is an open-ended request of the PI from the IRB; and should be a flashing neon sign to the IRB that this is a deferral.
  - To assess the risk and consent; the IRB needs to know:
    - Does the study describe who the controls will be? Healthy or stable on drug
    - Will they remain on current treatment/drug and add the study drug?
    - Are they hospitalized? Do they need to be?
    - Will there be frequent checks?

5. **OHRP:** 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); see example (5) in section D below for an alternative approach that would allow the IRB to approve the research with conditions);

IRB Minutes: "If all females must be of non-childbearing potential, it is unclear why the protocol includes a serum pregnancy test at screening. The master protocol seems to include contradictory information, indicating in Table 3.2 that a serum pregnancy test will be performed on all female subjects of childbearing potential.

- Example of an issue that should have been resolved prior to the meeting.

IRB Minutes: Please confirm that female subjects of childbearing potential are not eligible and that the pregnancy test provides an added level of protection beyond the planned FSH test and documented oophorectomy, hysterectomy, or tubal ligation.

- Either defer the study or state that approval excludes female subjects of childbearing potential from the study and state which test should be used to rule that out.

IRB Minutes: Please revise the text here accordingly.

- What is the revision being requests?
  - The IRB needs to include in the minutes and read to the members the exact wording that they are voting on.
  - Must write out the new wording requested and READ to the board or project on a screen.
  - Members should not vote on a change blindly.

IRB Minutes: Please confirm that if you will be performing the pregnancy tests, that the sponsor will pay for these."

- Good to confirm prior to the meeting; would need to defer if their response is sponsor will not pay.

6. **OHRP:** 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); see example (6) in section D below for an alternative approach that would allow the IRB to approve the research with conditions);

D.6. *For a randomized clinical trial comparing two types of surgical procedures, requiring that 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 administrator or other qualified IRB staff member to review the revised protocol and verify that the requested language regarding the process for soliciting informed consent of the prospective subjects was added to the protocol.* Or

Comment: No consenting subjects on the way to the OR and already under light sedation!

7. **OHRP:** 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)).

More Examples from UNC Minutes

Please revise to state that the blood sample is obtained to evaluate coagulation, chemistry, and hematology parameters indicative of overall health and safety (as indicated in able 3.2 of the Master Protocol), including to determine the subject meets (or continues to meet, as is the case with visits beyond baseline) all eligibility criteria.

The consent and master protocol state that the study drug and/or placebo is a capsule whereas this indicates it is an IV of four infusions. Please ***reconcile***. If IV infusion is correct, no more than one infusion per day should occur.

- If there is a disconnect between the consent and master protocol; then the IRB cannot just the risk:benefit ratio. This study needs to be deferred. Other issues: method of drug delivery is in question and dosing.

Adult Consent Form:

1. Please add the following language for genetic studies: **PERFECT**

Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

2. Since HIV screening will be done, please add the following communicable disease language: **PERFECT**

Under North Carolina law, confidentiality does not extend to certain communicable diseases, such as TB, HIV, hepatitis,or other illnesses that put others at risk. If the researchers become aware that subjects have such an illness, they are required to report it to state authorities.

3. Please review and revise the consent form for redundancy and length. **NOT PERFECT**

- **This must come back to the IRB for review.**
- **If you haven't seen it, then are you sure that you will be happy with this next version of the consent.**

Approval of Research with Conditions: OHRP Guidance (2010)

This guidance represents OHRP's current thinking on this topic and should be viewed as recommendations unless specific regulatory requirements are cited. The use of the word *must* in OHRP guidance means that something is required under HHS regulations at 45 CFR part 46. The use of the word *should* in OHRP guidance means that something is recommended or suggested, but not required. An institution may use an alternative approach if the approach satisfies the requirements of the HHS regulations at 45 CFR part 46. OHRP is available to discuss alternative approaches by telephone at 240-453-6900 or 866-447-4777, or by email at ohrp@hhs.gov.

Date: November 10, 2010

Scope: This document applies to non-exempt human subjects research conducted or supported by HHS. It provides guidance on the authority of institutional review boards (IRBs) to approve research with conditions. In particular, OHRP offers guidance on the following topics:

Target Audience: IRBs, investigators, HHS funding agencies, and others that may be responsible for the review, conduct, or oversight of human subjects research conducted or supported by HHS.

Regulatory Background:

An IRB must review proposed research, including proposed changes to previously approved research, at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas, except when expedited review is authorized (45 CFR 46.108(b) and 46.103(b)(4)). In order for research to be approved, it must receive the approval of a majority of those members present at the meeting (45 CFR 46.108(b)).

IRBs reviewing research have the authority to approve, require modifications in (to secure approval), or disapprove the research (45 CFR 46.109(a)).

An IRB may use the expedited review procedure to review either or both of the following:

1. Some or all of the research appearing on the list of categories of research that may be reviewed by the IRB through an expedited review procedure (see);
2. Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. (45 CFR 46.110).

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 following requirements are satisfied in accordance with HHS regulations at 45 CFR 46.111:

1. Risks to subjects are minimized (i) by using procedures which are consistent with sound research design and which do not

unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes;
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. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
3. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116.
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117.
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects

When applicable, IRBs must determine that the additional protections of subpart B (Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research), subpart C (Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects), or subpart D (Additional Protections for Children Involved as Subjects in Research) of 45 CFR part 46 have been met.

Guidance:

A. What actions can an IRB take when reviewing research?

Given the authorities that IRBs have under HHS regulations at 45 CFR 46.109(a), when conducting an initial or continuing review of a research study, or a review of proposed changes to a previously approved research study, an IRB can take any of the following actions:

1. Approve the research study or proposed changes either (a) as submitted without any conditions, or (b) with conditions (note that, as explained in section B below, when research is approved by the IRB with conditions at a convened meeting, further review by IRB at a subsequent convened meeting is not necessary);
2. Require modifications to secure approval and defer or table the research study or proposed changes for further review at a future date after the required modifications are submitted by the investigator; or
3. Disapprove the research study or proposed changes.

B. What does *IRB approval with conditions* mean?

In the course of initial or continuing review of research, or review of proposed changes to previously approved research, IRBs often request that investigators (a) make specified changes to the research protocols or informed consent documents; or (b) submit clarifications or additional documents. When doing this, depending on the circumstances, the IRB is either:

1. precluded from approving the research, as described in section C below; or
2. permitted to approve the research with conditions, as described in section D below.

By *IRB approval with conditions* (sometimes referred to as "conditional approval" or "contingent approval"), OHRP means that at the time when the IRB reviews and approves a research study (or proposed changes to a previously approved research study), 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.

C. 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.

When an IRB reviewing a research project at a convened meeting is unable to approve research because it cannot make the determinations required for approval, the IRB can either disapprove the project, or defer or table the project for further review at a future date. When deferring or tabling the project, the IRB, under its authority to require modifications in order for an investigator to secure approval, may require that the investigator (a) make changes to the protocol or informed consent documents, or (b) submit clarifications or additional documents prior to the next review. If the IRB defers or tables a research project, the research may not proceed until the IRB reviews the revised research project and approves it at a subsequent convened meeting.

When an IRB reviewing a research project under an expedited review procedure is unable to approve the project because the chairperson (or designated reviewer(s)) cannot make the determinations required for approval, the IRB chairperson (or designated reviewer(s)) can either refer the project to the IRB for further review and action at a convened meeting, or defer approval of the research project and require that the investigator (a) make changes to the protocol or informed consent documents, or (b) submit clarifications or additional documents prior to further review by the IRB chairperson (or designated reviewer(s)). Research may not be disapproved under an expedited review procedure (45 CFR 46.110(a)).

Examples of required changes or clarifications that generally would preclude the IRB from approving the research include the following:

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));
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); see example (5) in section D below for an alternative approach that would allow the IRB to approve the research with conditions);

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); see example (6) in section D below for an alternative approach that would allow the IRB to approve the research with conditions); or
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)).

D. What circumstances permit the IRB to approve research with conditions?

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.

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.**

When the IRB approves research with conditions, verification procedures must be included as part of the IRB approval process, under which the IRB chairperson (and/or other individual(s) designated by the IRB) will review responsive materials from the investigator required by the IRB, and determine whether the conditions of approval have been satisfied (45 CFR 46.102(h)). The IRB's verification that the investigator has satisfied all conditions of approval stipulated by the IRB helps to ensure that the investigator does not initiate any research that is different from what was approved by the IRB (45 CFR 46.102(h)).

Note that OHRP does not consider this verification process by the IRB chairperson or any other individual designated by the IRB to represent the review and approval of minor changes under an expedited review procedure. As a result, IRBs have significant flexibility regarding who may be designated to verify that conditions have been satisfied, including designation of someone other than an IRB member.

Individuals designated by the IRB to review responsive materials from the investigator and determine whether the IRB's conditions for approval have been satisfied should have appropriate expertise or qualifications. Depending upon the nature of the required conditions, the IRB could designate any of the following individuals or groups of individuals to determine that the conditions of approval have been satisfied:

- The IRB chairperson;
- Another IRB member or group of IRB members with particular subject matter expertise or experience;
- A consultant with particular subject matter expertise who is not an IRB member; and/or
- An IRB administrator or other qualified IRB administrative staff person, who need not be an IRB member.

For some conditions, the review of responsive materials from investigators will require medical, scientific, or other technical expertise. In such cases, the IRB should designate an individual having the appropriate expertise to review the responsive materials from the investigator; typically, this would be the IRB chairperson, another IRB member, or an expert consultant. For others conditions for which the investigator simply needs to make verbatim changes to the protocol or informed consent document or to submit a specific document, review of the responsive materials from investigators typically will not require any special expertise. In these cases, the IRB could designate an IRB administrator or other IRB administrative staff person to review the responsive materials from the investigator.

The following examples illustrate the types of conditions IRBs could stipulate when approving

research, as well as the type of individual who might be designated by the IRB to determine that the conditions of approval have been satisfied; these examples are not intended to be all-inclusive, nor are they intended to suggest that the type of individual designated in the example is either appropriate or necessary in all such circumstances:

1. Requiring submission of documentation of an endorsement letter from a department chair, as required by institutional policy, and designating an IRB administrator or other qualified 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 administrator or other qualified IRB staff member to review the revised informed consent document and confirm that the required corrections were made;
3. Requiring that a listed investigator provide a copy of his approved clinical privileges/hospital staff appointment document in order to confirm that 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 IRB administrator or other qualified IRB staff member to review this document and confirm that the clinical privileges of the listed investigator include authorization to perform such procedures.
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 of the form to a separate section under the heading "Compensation," and designating an IRB administrator or other qualified IRB staff member to review the revised informed consent document and verify the re-location;
5. Requiring that 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 administrator or other qualified 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 that 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 administrator or other qualified IRB staff member to review the revised protocol and verify that the requested language regarding the process for soliciting informed consent of the prospective subjects was added to the protocol.
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 administrator or other qualified 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 administrator or other qualified IRB staff member to review the revised informed consent document and verify the addition;
9. Requiring the addition to the informed 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 informed consent document and confirm that the description of the risks is satisfactory;
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 informed consent

document to be at an 8th grade comprehension level, and designating the IRB chairperson to review the revised informed consent document and ensure that risks are accurately described and understandable at an 8th grade comprehension level;

12. Requiring that 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 protocol (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.

E. How should the IRB handle changes to research that are proposed after the IRB has approved the research with conditions?

After research has been approved with conditions by the IRB, additional changes are sometimes proposed by the investigator or recommended by designated reviewers before all conditions have been satisfied and the protocol documents have been finalized. The process for handling such changes is the same as for any change that is proposed during the period for which IRB approval has already been given (see 45 CFR 46.103(b)(4)(iii)).

Protocol corrections that are only administrative in nature (e.g., correction of typographical and spelling errors in the protocol) would not need additional IRB review because OHRP does not consider such corrections to be changes to the research.

Changes to the research that are "minor" may be reviewed by the IRB chairperson or by another experienced reviewer designated by the chairperson from among the members of the IRB under an expedited review procedure in accordance with 45 CFR 46.110(b)(2). OHRP notes that under 45 CFR 46.110(c), all members of the IRB must be advised of any such minor changes that are approved under an expedited review procedure.

Changes to the research that are more than minor would require further review by the IRB at a convened meeting.

OHRP recommends that institutions adopt policies for determining the types of changes in previously approved research that constitute "minor" changes which can be approved under an expedited review procedure, in contrast to greater than minor changes which require review by the IRB at a convened meeting.

F. 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. (For additional guidance on determining the effective dates of IRB approval and continuing review dates, see OHRP's *Guidance on IRB Continuing Review of Research* at http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/index.html.) In these circumstances, no research study activities involving human subjects may be initiated until the conditions have been satisfied in the manner set forth by the IRB and the approval becomes effective.

Once the investigator has responded to the IRB's conditions, 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 investigator may submit additional revisions or material to the IRB for review by the designated reviewer(s) in an attempt to satisfy the IRB's conditions, or may choose to submit a modified research proposal to the IRB. If the investigator chooses not to submit any additional revisions or materials to the IRB for review by the designated reviewer(s), then the approval for the research activity would not become effective, and the investigator may not conduct the research study.

When someone other than the IRB chairperson is the designated reviewer and the designated reviewer and investigator are unable to agree on whether the responsive material provided to the IRB by the investigator satisfies the conditions of approval, OHRP recommends that the designated reviewer and investigator consult with the IRB chairperson or that the matter be referred to the convened IRB.

G. May an IRB approve some components of a proposed research study and defer taking action on other components at the time of initial review?

Yes, at the time of initial review an IRB may approve some components of a proposed research study and allow an investigator to initiate research activities only

related to those approved components, while deferring taking action on other components of the proposed study. In such circumstances, the IRB must ensure that the approved components of the research study are scientifically valid and satisfy all criteria required for IRB approval, even if the other components are never approved and conducted. The IRB may require that the investigator, in order for the investigator to secure approval for the unapproved components of the initially proposed research study, submit to the IRB for review (a) changes to the protocol or informed consent documents, or (b) clarifications or additional documents. The following example further illustrates this scenario:

1. The investigator proposes a research study involving the enrollment of subjects ages 12-65 years, including pregnant women.
2. Because the investigator did not provide sufficient information regarding the involvement of children and pregnant women, the IRB is unable to make the findings required for approval under subparts B and D of 45 CFR part 46. As a result, the IRB approves the research study for one year only for involvement of non-pregnant adult subjects, and the research may not involve pregnant women or children. Note that the IRB must ensure that the study as initially approved without inclusion of children or pregnant women is scientifically valid and satisfies all criteria for IRB approval under 45 CFR 46.111.
3. The IRB requires that the investigator, in order to secure approval for inclusion of pregnant women and children in the study, submit additional information necessary for the IRB to make the findings required under subparts B and subpart D of 45 CFR part 46.
4. The investigator subsequently submits sufficient information necessary for the IRB to make the determinations required under subparts B and D. The IRB reviews this information, makes the required determinations, and approves the involvement of children and pregnant women in the study. At this point, the investigator can begin enrolling pregnant women and children.

H. How do conditions on IRB approval at the time of continuing review, or at the time of review of proposed changes in previously approved research, affect ongoing research?

When approving research with conditions at the time of continuing review, or at the time of review of proposed changes to previously approved research, the IRB should be careful to specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions. For example, if at the time of continuing review the IRB requires the investigator to change the research protocol to include a specific new procedure for screening prospective subjects, the IRB could approve the research with the following condition: research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised protocol and verifies that the protocol includes the new screening procedure.

Likewise, if at the time of continuing review, or at the time of review of proposed changes to previously approved research, the IRB requires that the investigator within 30 days (a) change the informed consent document to include a description of a newly identified risk, and (b) submit a written plan for informing currently enrolled subjects about the new risk, the IRB could approve the research with the following condition: research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised informed consent document and verifies that the description of the new risk has been added. Alternatively, the IRB could stipulate that no further research activities involving human subjects (including activities of already enrolled subjects) may occur after the date of the IRB's continuing review or the review of the protocol changes until the investigator has submitted, and the designated IRB member has reviewed and accepted as satisfactory, the revised informed consent document *and* the written plan for informing currently enrolled subjects about the new risk.

Note that OHRP would not consider such suspensions of subject enrollment or of activities involving already enrolled subjects at the time of continuing review to be suspensions of IRB approval that needs to be reported to appropriate institutional officials, the head (or designee) of the agency conducting or supporting the research, and OHRP under HHS regulations at 45 CFR 46.103(a) and 46.103(b) (5).

I. What must the IRB records include regarding the documentation of conditions of IRB approval of research?

When the IRB approves research with conditions, the IRB must document, 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, the following:

1. All conditions that must be satisfied by the investigator (45 CFR 46.102(h), 45 CFR 46.109(d), and 45 CFR 46.115);
2. The date when the IRB chairperson (and/or other individual(s) designated by the IRB) determines that all conditions of IRB approval have been satisfied, the date when initial approval becomes effective, and the date by which continuing review must occur;
3. In the case of initial review, any conditions under which some research activities may be initiated (for example, the investigator may initiate research in non-pregnant adults, but not in pregnant women or children); and
4. In the case of continuing review and the review of proposed changes to previously approved research, any conditions that need to be satisfied before an investigator can continue particular research activities related to those conditions (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 (45 CFR 46.115(a) (4)).

Copies of all research proposals reviewed by the IRB and approved sample consent documents, including any revised protocol or informed consent documents submitted by the investigator in order to satisfy the conditions of approval stipulated by the IRB, also must be maintained in the IRB records (45 CFR 46.115(a)(1)).

If you have specific questions about how to apply this guidance, please contact OHRP by phone at (866) 447-4777 (toll-free within the U.S.) or (240) 453-6900, or by e-mail at ohrp@hhs.gov.

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