

**HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &
IMPLEMENTATION**

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

SOP Number: 7

**SOP Title: REQUIREMENTS FOR THE ETHICAL AND REGULATORY REVIEW OF
RESEARCH BY NIH INSTITUTIONAL REVIEW BOARDS (IRBs)**

**Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB
Chairs, IRB Administrators, Protocol Navigators**

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SOP 7 – REQUIREMENTS FOR THE ETHICAL AND REGULATORY REVIEW OF RESEARCH BY NIH INSTITUTIONAL REVIEW BOARD (IRBs)

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SOP 7 – REQUIREMENTS FOR THE ETHICAL AND REGULATORY REVIEW OF RESEARCH BY NIH INSTITUTIONAL REVIEW BOARD (IRBs)

7.1 PURPOSE

The purpose of this SOP is to assure that all NIH IRBs follow the same meeting procedures.

7.2 POLICY

All non-exempt human subjects research must be reviewed and approved by an NIH IRB, either through expedited review or review at a convened IRB meeting, prior to commencement. (See SOP 7A - Requirements for Expedited Review of Research by NIH Institutional Review Boards).

The following procedures, including quorum, voting requirements and IRB review standards apply to all convened NIH IRB meetings.

7.3 TIMING OF IRB MEMBERS' RECEIPT OF IRB MEETING AGENDAS AND OTHER MATERIALS

Initial Reviews, Continuing Reviews and Amendments: At least five days prior to the meeting, IRB members and reviewers (see **7.6.2**, below, Primary and Secondary Reviewer Mechanism) receive agendas, including the complete packet of attachments, designated for initial and continuing reviews and amendments described at SOP 3 - Management and Administrative Operations of the IRB.

7.4 ATTENDANCE OF NON-IRB MEMBERS (GUESTS) AT IRB MEETINGS

IRB meetings are not open to the public. However, authorized NIH staff, e.g., from OHSRP, and guests may attend the meeting, as follows:

- A. The IRB may request that investigators attend the meeting to present their protocols or provide information pertaining to an IRB concern. The investigator may include members of the research team, if approved by the IRB. These individuals will be excused at the time of executive session (see **7.14** below) for discussion and voting.
- B. The IRB may request that a non-member provide consultation to assist in review of a protocol(s) according to SOP 2 - IRB Membership and Structures.

- C. Individuals who are affiliated with NIH may observe IRB meetings, at the discretion of the Chair, if the reason for the observation is training related to human subjects research protections. For purposes of this SOP, individuals are affiliated with the NIH if they appear in the NIH enterprise directory (NED) and/or are at NIH pursuant to a written agreement, e.g. training MOU or training letters of agreement. Affiliated individuals should ask the Chair in advance of the meeting for permission to attend, either directly or through the person responsible for the training. The Chair may deny the request if s/he does not consider the request to be consistent with the NIH training mission.
- D. A written statement attesting to confidentiality of the proceedings will be signed by guests. This statement may be on the sign-in sheet of the meeting.
- E. An investigator may ask the Chair, at least 24 hours prior to a meeting, that a representative accompany him or her if the IRB is discussing allegations of non-compliance. The investigator should identify whether the individual will be acting as legal counsel. If so, the NIH Office of General Counsel should be informed. The IRB reserves the right to go into executive session and exclude the researcher and representative from that portion of the meeting.
- F. NIH-affiliated individuals who wish to collect research data about IRB operations at a convened meeting may only do so according to an IRB-approved protocol or an OHSRP exemption, and with the permission of the Chair and the IRB.
- G. Other NIH staff and personnel, at the request or direction of the OHSRP or the DDIR, such as representatives of the Office of the General Counsel or the IC.
- H. Rarely, exceptions to this list may be made by the DDIR or the Director, OHSRP.

7.5 QUORUM

A quorum of members must be present for an IRB to conduct a convened IRB meeting and approval must be by a majority vote of the quorum. OHSRP's expectation is that a non-affiliated member and a member representing the perspective of research participants will be present at a majority of the IRB meetings. On an annual basis, IRBs will report to OHSRP the number of non-affiliated members and the number of members representing the perspective of research participants present at each IRB meeting.

7.5.1 DEFINITION OF THE MEETING QUORUM

A quorum requires a simple majority (more than half) of the voting members to be present. For example, for a membership of 10, the quorum to convene the meeting is 6. For an 11-member board, the quorum would be 6. In addition, one of the members present must have his/her primary focus in nonscientific areas. The IRB Chair counts in determining the meeting quorum.

7.5.2 MAINTENANCE OF THE QUORUM

- A. During the convened IRB meeting, the IRB staff monitors the members present to ensure that quorum is maintained throughout the meeting.
- B. Should the IRB lose the quorum during the meeting (e.g., those with conflicts are excused, early departures, loss of all members whose primary concerns are in nonscientific areas), no further votes will be conducted, nor actions requiring a quorum taken, until the quorum is restored. If necessary, the meeting will be adjourned and any actions not voted upon because of lack of a quorum will be postponed until the next convened IRB meeting.

7.6 CONVENED IRB MEETING PROCEDURES

7.6.1. REVIEW REQUIREMENTS

- A. All IRB members receive all the materials listed in SOP 3 - Management and Administrative Operations of the IRB for initial reviews, continuing reviews, amendments and study closure and are expected to do an in-depth review of these documents, except in cases where a primary or secondary reviewer (see **7.6.2** below) will review and provide a summary of the materials to the other IRB members.
- B. The IRB will use the IRB Protocol Review Standards (**Appendix A**) as a tool to assist in ensuring that all regulatory and NIH policy requirements are addressed during its review of protocols.

7.6.2 PRIMARY REVIEWER OR PRIMARY AND SECONDARY REVIEWER MECHANISM

- A. This section only applies if the IRB uses a primary reviewer or a primary and secondary reviewer system (meaning that the IRB uses two reviewers for each review). Each IRB is required to keep OHSRP informed in writing about whether or not it uses such a system.

- B. A primary or primary and secondary reviewer system may be used for any or all reviews at a convened IRB meeting, as approved by the IRB.
- C. Primary or secondary reviewers will be assigned by the Chair, or a designee, to specific protocols based on factors including but not limited to relevant professional expertise, subject matter of the research and prior experience with review of similar projects. Protocols will not be assigned to a member who is associated with the research or has some other conflict of interest.
- D. Primary or secondary reviewers may work with the investigator before the IRB meeting to resolve certain issues that emerged from the reviewer's evaluation.
- E. Primary or secondary reviewers are responsible for performing an in-depth review of all pertinent documents, including the Investigators Brochure (if applicable), providing a summary to other IRB members, and for leading the discussion at the convened IRB meeting.
- F. If the primary reviewer assigned to the protocol will be absent from the convened IRB meeting the protocol will be reassigned to another reviewer prior to the meeting.
- G. All other IRB members should at least receive a protocol summary (of sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111), the proposed informed consent document, and any recruitment materials, including advertisements intended to be seen or heard by potential subjects. In addition, the complete documentation should be available to all members for review.

7.7 PRE-IRB SCIENTIFIC REVIEW

Prior to NIH IRB review, NIH requires that all intramural research protocols involving human subjects undergo review of scientific content by a scientific review process established by the Institutes and Centers (ICs). Clinical Directors may decide that pre-IRB scientific review is not necessary for natural history and training protocols.

A copy of the IC scientific review and approval (when applicable) is part of the electronic application submitted by PIs for initial review (see SOP 8 - Procedures and Required Documentation for Submission and Initial Review of Protocols).

The ICs are required to keep a current copy of their procedures for scientific review on file with OHSRP.

7.8 CRITERIA FOR APPROVAL OF HUMAN SUBJECTS RESEARCH

In order to approve research, NIH IRBs shall determine, and document in their minutes, that all of the following criteria are met in accordance with 45 CFR 46.111 and 21 CFR 56.111. In addition to these criteria, local laws should be taken into consideration.

- A. Risks to subjects are minimized by (a) using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (b) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- B. 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.
- C. Selection of subjects is equitable (see SOP 13 - Recruitment, Selection and Compensation of Research Subjects). 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 (see SOP 14A - Research Involving Vulnerable Subjects (General Considerations)).
- D. 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 Federal and state regulations (including 45 CFR § 46.116) and NIH policies and procedures (see SOP 12 - Requirements for Informed Consent).
- E. Informed consent will be appropriately documented in accordance with, and as required by, Federal and state regulations (including 45 CFR § 46.117) and NIH policies and procedures (see SOP 12 - Requirements for Informed Consent).

- F. The research plan makes adequate provisions for on-going review and for monitoring the data collected to ensure the safety of subjects (see SOP 9 - Continuing Review by the Convened IRB).
- H. There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data during and after their involvement in the research (see SOP 18 - Privacy and Confidentiality).
- I. 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 (see SOP 13 - Recruitment, Selection and Compensation of Research Subjects and SOP 14A - Research Involving Vulnerable Subjects (General Considerations)).
- J. The IRB is responsible for assuring that investigators and research staff are qualified by education, training, and experience needed to perform their delegated roles in conduct of the study. Since NIH HRPP Training requirements are specific to the nature of the research to be conducted and the role of the research staff member on the study; the IRB must review the training for investigators and research staff on a protocol-by-protocol basis and determine that the training requirements have been met as a condition for approval. For more information see SOP 25 - Training Requirements for the NIH Human Research Protection Program (HRPP).

The NIH IRB Protocol Review Standards (**Appendix A**) should be available at the IRB meeting for the PI or designee and IRB members to review when addressing the approval criteria listed above.

7.9 IRB DETERMINATIONS OF RISK AND BENEFIT

Please refer to **Appendix A** to this SOP for a summary of IRB requirements pertaining to risk/benefit determinations for various population groups as research subjects.

7.10 PERIOD OF APPROVAL

7.10.1 FREQUENCY OF REVIEW

At the time of initial and continuing review, the IRB will make a determination regarding the frequency of review of the research studies. All studies will be reviewed by the IRB at intervals appropriate to the degree of risk but not less

than once per year. In some circumstances, a shorter review interval (e.g. biannually, quarterly, or after accrual of a specific number of participants) may be required. The meeting minutes will reflect the IRB's determination regarding the frequency of review (see SOP 4 - Human Research Protection Program (HRPP) Documentation and Records).

7.10.2 CRITERIA FOR REVIEW MORE OFTEN THAN ANNUALLY

The IRB may require continuing review more often than annually in order to protect the rights and safeguard the welfare of research subjects. The following factors may also be considered when determining which studies require review more frequently than annually:

- A. The IRB's previous experience with the investigators (i.e. a history of serious or continuing non-compliance on the part of the Principal Investigator (PI), other investigators, or research staff.)
- B. The nature, probability, and magnitude of anticipated risks to subjects.
- C. The medical condition of the proposed subjects, before and during participation in the research.
- D. The involvement of vulnerable populations likely to be subject to coercion or undue influence.
- E. The overall qualifications and specific experience of the PI and other members of the research team in conducting similar research.
- F. The nature and frequency of adverse events in similar research at NIH and other institutions as known to the IRB.
- G. The nature of the research that might make unanticipated problems more likely.

7.11 EFFECTIVE DATE OF INITIAL APPROVAL

- A. For a study unconditionally approved by the IRB (i.e., without stipulations), the approval period starts on the date the convened IRB approved the research activity.
- B. For a study approved with stipulations, the effective date of approval is the date on which the IRB Chair (or designee) reviewed and accepted as satisfactory the investigator's response to the stipulations. (see SOP 9 - Continuing Review by the Convened IRB).

- C. The IRB may approve implementation of parts of the protocol pending an investigator's submission of clarifications or stipulated changes to unapproved parts of the protocol or submission of additional documents that will enable the IRB to approve the full protocol.

7.12 REVIEW OF UNANTICIPATED PROBLEMS AND NON-COMPLIANCE

See SOP 16 - Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations and SOP 16A - Allegations of Non-compliance with Requirements of the NIH Human Research Protection Program (HRPP).

7.13 INDEPENDENT VERIFICATION THAT NO MATERIAL CHANGES HAVE OCCURRED

7.13.1 INDEPENDENT VERIFICATION

The Federal regulations (45 CFR 46.103(b)(4)(ii)) acknowledge that protecting the rights and welfare of subjects may sometimes require that the IRB verify independently, utilizing sources other than the investigator, that no material changes occurred since previous IRB review.

7.13.2 VERIFICATION FROM OUTSIDE SOURCES

The IRB will determine if verification from outside sources is necessary including, but not limited to, studies that meet any of the following criteria:

- A. Cooperative studies, or other multi-center research.
- B. Studies where concern about possible material changes occurring without IRB approval has been raised based on information provided in continuing review reports or from other sources.
- C. Studies conducted by PIs who have a history of failure to comply with Federal regulations and/or the requirements or determinations of the IRB.
- D. Studies that are subject to internal audit.

7.13.3 ADDITIONAL FACTORS

The following factors may also be considered when determining which studies require independent verification:

- A. The probability and magnitude of anticipated risks to subjects.
- B. The likely medical condition of the proposed subjects.
- C. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.

7.13.4 TIMING

When the IRB makes determinations about the need for independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review, review of amendments and/or unanticipated problems.

7.13.5 CORRECTIVE ACTION

If any material changes have occurred without prospective IRB review and approval, the IRB will decide what corrective action should be taken (see SOP 16A - Allegations of Non-compliance with Requirements of the NIH Human Research Protection Program (HRPP)).

7.14 IRB EXECUTIVE SESSIONS

When the IRB goes into executive session to make decisions regarding protocols, continuing reviews, amendments and other actions and to vote, only IRB members, IRB administrative staff and OHSRP staff remain in the room. Guests may remain at the discretion of the IRB Chair or the DDIR. IRB members with a conflict of interest in connection with specific protocols will be recused, i.e., leave the room and do not vote.

7.15 IRB VOTING

7.15.1 VOTING REQUIREMENTS

- A. Each regular member, including the Chair and Vice Chair, and each alternate who is substituting for a regular member, has one vote.
- B. Protocol approval and the approval of any motion, requires the vote of a

- simple majority (more than half) of the voting members who are present.
- C. The Chair and Vice Chair count towards the quorum, unless recused, and either vote or abstain from voting on all actions for which votes are taken. Chairs and Vice Chairs will recuse themselves, as appropriate, when conflicts of interest exist.
 - D. Consultants do not vote (see SOP 2 - IRB Membership and Structures).
 - E. A vote that is cast by an individual on behalf of an IRB member is permitted only when that individual is an appointed alternate for an IRB member or category of members (see SOP 2 - IRB Membership and Structures).
 - F. If circumstances require members' participation by telephone or video conference, approval of the IRB Chair must be obtained in advance. Members attending by telephone- or video-conference count towards the quorum and may vote only if (1) they have received all pertinent material prior to the meeting and (2) they can participate actively and equally in the discussion of the research study. The IRB minutes must document that method of attendance, if not in person (see SOP 4 - Human Research Protection Program (HRPP) Documentation and Records).
 - G. Members with a real or perceived conflict of interest may not participate in IRB deliberations and will be required to leave the room during the IRB discussion and vote. They may be asked to provide information prior to deliberations but cannot be included in the quorum.

7.15.2 VOTING ON IRB ACTIONS

After discussion, the IRB may vote to take one of the following actions or make a determination when appropriate. (For determinations, see, for example, see SOP 16 - Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations and SOP 16A - Allegations of Non-compliance with Requirements of the NIH Human Research Protection Program (HRPP). These votes may be by show of hands or by written ballot, which may be secret. Actions include:

- A. **Unconditional Approval:** The IRB may approve protocol/continuing review/amendments, etc., without adding stipulations (conditions) and the study may begin/continue immediately after receiving all other required institutional approvals.
- B. **Approval with Stipulations:** The IRB may approve research with stipulations (conditions) if, given the scope and nature of the stipulations, the IRB is able, based on the assumption that the stipulations are

satisfied, to make all of the determinations required for approval under the HHS regulations 45 CFR 46.111 and, if applicable, subparts B, C, or D of 45 CFR 46.

1. In order to satisfy the IRB's stipulations the PI must:
 - a. Make the IRB-stipulated changes to the research protocol and/or informed consent document.
 - b. Confirm specific assumptions or understandings on the part of the IRB regarding how the research will be conducted as described by the investigator at his/her presentation of the protocol to the IRB.
 - c. Submit any additional documents requested to enable the IRB to approve the protocol.
 2. The following individuals may approve the investigator's response to stipulations:
 - a. The IRB Chair.
 - b. Another IRB member or group of IRBs members with appropriate subject matter expertise or experience designated by the Chair.
- C. **Deferred:** This term will be used when the protocol is not approved and the stipulations will require additional re-submission of the protocol by the PI and re-review by the convened IRB at a later time in order to determine whether to grant approval.
- D. **Tabled:** The IRB determines that it does not have sufficient information to approve the protocol.
- E. **Disapproval:** The IRB determines that it cannot approve a study as submitted.

7.16 NOTIFICATION OF IRB DECISIONS TO THE PI

The IRB notifies investigators in writing of its decision to approve or disapprove the proposed research activity, or of stipulations required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

7.17 CONFIDENTIALITY OF PROCEEDINGS

IRB Members, staff, and guests are required to respect the confidentiality of the IRB deliberations and decisions. Deliberations and decisions should not be disclosed to the Principal Investigator or others outside the IRB unless in connection with official duties and directed by policy or law.

7.18 DOCUMENTATION OF IRB ACTIONS

The IRB communications with the PI and the IRB minutes will comply with IRB records requirements at SOP 4 - Human Research Protection Program (HRPP) Documentation and Records, including what stipulations, if any, must be responded to by the investigator (see **Section 7.19.2**).

7.19 COMMUNICATIONS BETWEEN THE IRB AND THE PRINCIPAL INVESTIGATOR

7.19.1 REQUEST FOR MORE INFORMATION

When needed, the IRB may request additional information in writing from Principal Investigators before the meeting. IRB decisions and stipulations are conveyed to the Principal Investigator in writing within two weeks after the meeting. Principal Investigators are responsible for notifying Associate Investigators and sponsors of the IRB's decisions.

7.19.2 PI RESPONSE TO STIPULATIONS

Investigators must respond to stipulations within 30 days of receipt. The response can include a request for extension of that deadline, which will be considered by the IRB Chair on a case-by-case basis only for new studies and for amendments that do not impact the safety of enrolled subjects.

Investigators may not initiate the protocol until IRB approval for implementation (in part or in full) has been granted. At the NIH Clinical Center, protocols may not start until also approved by the Director, Clinical Center. The Deputy Director Intramural Clinical Research (DDICR) approves protocols conducted at sites other than the Clinical Center. The CC Office of Protocol Services sends the PI a notification when such approvals have occurred.

7.20 RECONSIDERATION OF THE IRB'S DECISIONS

If a Principal Investigator disagrees with a decision made by the IRB, he/she has the option to ask the IRB to reconsider its review and is expected to work

collegially with the IRB to resolve the issue. The request for reconsideration should be accompanied by an explanation of the reasons why the IRB determination should be reconsidered.

7.21 ADDITIONAL CONSIDERATIONS REGARDING NIH IRB RESEARCH REVIEW

- A. A research study submitted to one NIH IRB for review may not be submitted to a different NIH IRB either at the same time or subsequently. If the PI transfers to another Institute, the appropriateness of transferring the study to another IRB will be evaluated by appropriate officials in the respective ICs.
- B. NIH may elect not to conduct research that has obtained IRB approval. NIH may not conduct human subjects research if the protocol has been disapproved by an IRB.

Because the Institutional Official (the DDIR) is responsible for policies and procedures followed by the NIH HRPP, including its IRBs, he may review IRB decisions to ensure that the IRB's decision-making processes are appropriate (for example, it follows NIH HRPP SOPs, etc.). If he has concerns about these IRB processes and procedures, he may request IRB reconsideration of the issue/decision. However, if an IRB disapproves research, the DDIR cannot permit the research to move forward/implement the research

REFERENCES

- A. OHRP Guidance on Written IRB Procedures:
<http://www.hhs.gov/ohrp/policy/irbgd107.pdf>
- B. OHRP Guidance on IRB Approval of Research with Conditions:
<http://www.hhs.gov/ohrp/policy/conditionalapproval2010.html>

LIST OF APPENDICES

Appendix A: NIH IRB Protocol Review Standards

APPENDIX A: NIH IRB PROTOCOL REVIEW STANDARDS: A REVIEW TOOL FOR IRB MEMBERS AND PRINCIPAL INVESTIGATORS

Sample Requirements for IRB Protocol Review and Discussion

SECTION I – REGULATORY CRITERIA FOR IRB APPROVAL FOR NEW PROTOCOLS

(To be used by the Principal Investigator at the initial protocol presentation to the IRB)

Sample regulatory review requirements to be addressed for initial protocols by the PI at the convened IRB meeting	Suggested questions for IRB discussion
<p>1. The proposed research design is scientifically sound & will not unnecessarily expose subjects to risk.</p>	<p>a) Is the hypothesis clear? Is it clearly stated? b) Is the study design appropriate to prove the hypothesis? c) Will the research contribute to generalizable knowledge and is it worth exposing subjects to risk?</p>
<p>2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of knowledge that may reasonably be expected to result. Risks to subjects include physical, psychological, social, legal and socioeconomic risks.</p>	<p>(a) What does the PI consider the level of risk/discomfort/inconvenience to be? (See Attachment 1, risk assessment guide attached to this form). (b) Does the IRB agree with the PI’s risk assessment? (c) Is there prospect of direct benefit to subjects? (See Attachment 1, benefit assessment guide attached to this form.) (d) Are risks reasonable in relation to anticipated benefits, if any to subjects?</p>
<p>3. Risks to subjects are minimized.</p>	<p>Do data and safety monitoring plans make adequate provision for monitoring the data collected to ensure the safety of subjects?</p>

<p>4. Subject selection is equitable taking into account the purpose and setting of the research</p>	<p>a) Who is to be enrolled? Men? Women? Ethnic minorities? Children (rationale for inclusion/exclusion addressed)? Seriously-ill persons? Adults who may be unable to give consent? Healthy volunteers? b) Are these subjects appropriate for the protocol?</p>
<p>5. Additional safeguards are included for subjects likely to be vulnerable to coercion or undue influence.</p>	<p>a) Are appropriate regulatory or other protections in place for vulnerable subjects, e.g., pregnant women, fetuses, socially- or economically-disadvantaged, prisoners, adults who may be unable to give consent?</p>
<p>6. Informed consent is obtained from research subjects or their legally authorized representative(s) as required by 45 CFR 46.116 and appropriately documented in accordance with, and to the extent required by 45 CFR 46.117 and for FDA-regulated research, 21.CFR 50.</p>	<p>a) Does the informed consent document include the eight required elements? b) Is the consent document understandable to subjects? c) Who will obtain informed consent (PI, nurse, other?) & in what setting? d) If appropriate, is there a children’s assent? e) (e) Is the IRB requested to waive or alter any informed consent requirement?</p>
<p>7. Subject privacy & data confidentiality are maximized.</p>	<p>a) Will personally-identifiable research data be protected to the greatest extent possible from unauthorized access or use? b) Are any special privacy & confidentiality issues appropriately addressed in the research plan, e.g., distribution of identifiable genetic information?</p>
<p>ADDITIONAL CONSIDERATIONS</p>	
<p>1. Ionizing radiation.</p>	<p>If ionizing radiation is used in this protocol is it medically indicated or for research use only?</p>

2. Collaborative research.	Is this domestic or international collaborative research? If so, are FWAs or written agreements required (such as a Reliance Agreement or CRADA)?
3. FDA-regulated research	Does the research involve the use of a product that is subject to FDA regulation? If so, is an IND or IDE involved in this protocol? Is an IND/IDE required? (For help in determining the need for an IND/IDE see SOP 15).
4. Duration of approval	Does the protocol require review more frequently than annually?

SECTION II –POINTS TO CONSIDER BY THE IRB AT CONTINUING REVIEW

Requirements to be addressed for new protocols by the PI at the convened IRB meeting	Suggested questions for IRB discussion
1. Regulatory criteria.	After any changes, will the protocol still meet all of the regulatory and policy criteria necessary for an IRB to approve research (46.111).
2. Continuing review requirements	Have the relevant continuing review requirements been followed as set forth in SOP 9 - Continuing Review by the Convened IRB.
3. Changes in previously approved research	Does the protocol require verification from sources other than the investigator(s) that no material changes have occurred since the previous review? (Material change means any change that would affect the determination of whether the research meets the regulatory criteria for IRB approval.)
4. Research risks	Has any information appeared in the literature or evolved from this or similar research that might change the IRB's initial evaluation of the risk/benefit analysis of human subjects involved in this protocol?
5. Significant new findings	Are there any significant new findings that might affect the subjects' willingness to continue participation in research?
6. Protocol recruitment	Is the protocol meeting its recruitment goals?
7. Research progress and rationale for continuing the study	Is the research progressing as proposed/expected? Should the study continue?
8. Unanticipated problems (see Section III, below)	Have there been any unanticipated problems involving risks to subjects since the last review? If so, is

	amendment of the protocol required? Have any new risks been identified in the summary of adverse events, protocol deviations, UPs or UADEs?
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SECTION III –POINTS TO CONSIDER FOR AMENDMENTS

<p>Requirements to be addressed for new protocols by the PI at the convened IRB meeting</p>	<p>Suggested questions for IRB discussion</p>
<p>1. Regulatory criteria.</p>	<p>After any changes, will the protocol still meet all of the regulatory and policy criteria necessary for an IRB to approve research, including risk benefit analysis, consent, etc.</p>
<p>2. Amendment requirements</p>	<p>Have the relevant amendment requirements been followed as set forth in SOP 10 - Amendments to IRB-approved Research.</p>

SECTION IV - POINTS TO CONSIDER BY THE IRB WHEN REVIEWING UNANTICIPATED PROBLEMS OR PROTOCOL DEVIATIONS WHETHER REPORTED PROMPTLY AS PROBLEMS OR IN AGGREGATE AT TIME OF CONTINUING REVIEW

Requirements to be addressed for new protocols by the PI at the convened IRB meeting	Suggested questions for IRB discussion
<p>Definition of an Unanticipated Problem (UP) An unanticipated problem is any incident, experience or outcome that:</p> <p>a) Is unexpected in terms of nature, severity or frequency given (i) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (ii) the characteristics of the subject population being studied, AND</p> <p>b) is related or possibly related to participation the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research), AND (c) suggests that the research places subjects or others at a <i>greater risk of harm</i> (including physical, psychological, economic or social harm) than was previously known or recognized.</p>	<p>a) Is the incident, experience or outcome unexpected given the research procedures that are described in the IRB-approved research protocol, consent, or other study documents, and the characteristics of the subject population being studied?</p> <p>b) Is the incident, experience or outcome related or possibly related to participation in research?</p> <p>c) Does the incident, experience or outcome suggest that the research places subjects or others at greater risk of harm?</p> <p>If yes:</p> <p>d) Is there a pattern of UPs/protocol deviations (PDs)?</p> <p>e) Is any action required on the part of the IRB or the PI as a result of UPs/PDs (e.g., change in protocol procedures/change in consent document)?</p> <p>f) Should the UP be reported to OHSRP?</p> <p>If no: Is any further action required on the part of the IRB or PI?</p>
<p>Definition of a Protocol Deviation (PD) Any change, divergence, or departure</p>	<p>a) Is this PD also a UP?</p> <p>b) Does this PD represent serious or continuing non-compliance? (see</p>

<p>from the IRB-approved research protocol. PDs may be serious or non-serious. For examples of PDs see SOP 16 - Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations</p>	<p>SOP 16A) c) Will the PD result in change to the risk/benefit analysis or to the protocol or informed consent? (d) Should the PD be reported to OHSRP?</p>
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SECTION V - RISK/BENEFIT ASSESSMENT GUIDE

The IRB should ensure that 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.

Regulatory definition of minimal risk: Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research 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 (45 CFR 46.102(h)(i)). (Note that minimal risk is defined differently for prisoners, see 45 CFR 46.303(d).)

Regarding the basic requirements for informed consent, 45 CFR 46.116(a)(3) requires : A description of any benefits to the subject or to others which may reasonably be expected from the research. Note that money or other compensation for participation in research is not considered to be a benefit, but rather compensation for research-related inconveniences

The “risk/benefit” analysis will vary depending on the population of research subjects. For example, people with certain medical conditions may ordinarily encounter different risks in daily life than healthy volunteers. If a protocol involves many different types of subjects, the risk evaluations may be different for each group. The following requirements apply to specific population groups:

I. RISK/BENEFIT CATEGORIES APPLICABLE TO RESEARCH WITH ADULTS

IRBs must select one of the following risk categories for adults (However, please refer to Section V below, not this section, for research activities pertaining to adults who are unable to consent or may be unable to consent.):

1. Research not involving greater than minimal risk.

2. Research involving greater than minimal risk to subjects.

The benefit categories applying to adults are as follows:

1. No prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition:
2. The research involves the prospect of direct benefit to the individual subjects.

II. RISK/BENEFIT CATEGORIES APPLICABLE TO RESEARCH WITH CHILDREN

The following risk categories apply to research involving children and the IRB must select one of these categories:

1. Research not involving greater than minimal risk. (45 CFR 46.404)
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. (45 CFR 46.405)
3. 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. (45 CFR 46.406)
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (CFR 46.407)

For more information about participation of children in research, see SOP 14D-Research Involving Children.

III. RISK /BENEFIT REQUIREMENTS INVOLVING RESEARCH WITH PREGNANT WOMEN, FETUSES, OR NEONATES

45 CFR 46.204 contains the following requirements involving risk/benefit requirements when IRBs review for research activities involving pregnant women or fetuses:

- (a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant

women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

- (b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
- (c) Any risk is the least possible for achieving the objectives of the research

For more information about involvement of pregnant women, fetuses and neonates in research, see SOP 14B - Research Involving Pregnant Women, Human Fetuses and Neonates.

IV. RISK DEFINITION SPECIFIC TO RESEARCH INVOLVING PRISONERS

The definition of minimal risk for prisoner research at 45 CFR 46.303(d) differs from the definition of minimal risk that applies to other research NOT involving prisoners. The general definition is provided at the top of this guide. However, when prisoners are research subjects, the following standard must be applied: "Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research 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" (see 45 CFR 46.102(i)).

For more information about involvement of prisoners in research, see SOP 14C - Research Involving Prisoners.

V. RISK/BENEFIT CATEGORIES FOR ADULTS WHO ARE OR MAY BE UNABLE TO CONSENT

SOP 14E - Research Involving Adults Who Are or May Be Unable to Consent, states that IRBs may approve research with adults who are or who may be unable to consent ONLY for specific categories, related to risk: Furthermore, SOP 14 E relates the risk assessment by an IRB to the specific requirements for a surrogate decision maker. SOP 14E.6.2 - NIH IRB Determinations of Allowable Categories of Research, states as follows:

- A. **Research not involving greater than minimal risk.** Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research 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.

- B. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.** Inclusion of adults who cannot consent may be approved in this category only when an NIH IRB determines that the prospect of benefit to the subjects justifies the risks and burdens to them and the risk-benefit profile of the research is at least as favorable for the subjects as the risk-benefit profile of available alternatives.
- C. Research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects.** An NIH IRB must approve this category of research, and the PI must comply with the requirements set forth in Attachment 2 to SOP 14E - Research Involving Adults Who Are or May Be Unable to Consent.
- D. Research involving more than a minor increase over minimal risk and no prospect of direct benefit to individual subjects.**
1. In order to approve this research, an NIH IRB must fulfill the other requirements of this SOP and determine and document that the knowledge to be obtained:
 - a. is of vital importance
 - b. cannot reasonably be obtained by studying adults who can consent, and
 - c. cannot be obtained in a way that poses less risk.
 2. Additional NIH review and approval: After an NIH IRB approves this research, additional review shall be conducted by the NIH Deputy Director for Intramural Research (DDIR) who will convene a panel of independent Federal employee experts. The DDIR can approve research in this category only if the panel finds that the knowledge to be obtained is of:
 - a. vital importance
 - b. cannot reasonably be obtained by studying adults who can consent, and
 - c. cannot be obtained in a way that poses less risk.

For more information about involvement of adults without the capacity to consent in research, see SOP 14E - Research Involving Adults Who Are or May Be Unable to Consent.