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

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

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**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**

Approval: Michael M. Johnson 6/11/13
Deputy Director for Intramural Research Date

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RESEARCH BY NIH INSTITUTIONAL REVIEW BOARDS (IRBS)**

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SOP 7 REQUIREMENTS FOR THE ETHICAL AND REGULATORY REVIEW OF RESEARCH BY NIH INSTITUTIONAL REVIEW BOARDS (IRBS)

7.1 PURPOSE

This policy provides basic requirements for IRB review of human subjects research.

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.

7.3 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. Clinical Directors may decide that pre-IRB scientific review is not necessary for natural history and training protocols. The Institutes and Centers are required to keep a current copy of their procedures for scientific review on file with OHSRP.

7.4 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 SOP14A, "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 from Research Subjects").
- 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).
- 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" and SOP 17, "Data and Safety Monitoring").
- G. 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").

- H. 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”).

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.

7.5 IRB DETERMINATIONS OF RISK AND BENEFIT

At the time of initial and continuing review and amendments, the levels of risk and potential benefit to subjects are determined by the IRB and appropriately documented in the IRB minutes.

- A. For adults who have the capacity to consent, the following risk designations are used. For subjects unable to consent, see SOP 14E (“Research Involving Adults Who Are or May be Unable to Consent”) for the risk categories for subjects who are unable to consent.
 - 1. The research involves no more than minimal risk to subjects, or
 - 2. The research involves more than minimal risk to subjects.
- B. For adults, the following benefit designations are used:
 - 1. The research involves no prospect of direct benefit to individual subjects, or
 - 2. The research involves the prospect of direct benefit to individual subjects.
- C. For children, the IRB will make a determination with regard to whether the study falls within 45 CFR 46.404, 46.405, 46.406 or 46.407. See SOP 14D (“Research Involving Children”).

The following risk designations are used.

1. The research involves no greater than minimal risk to subjects, or
2. The research involves greater than minimal risk to subjects, or
3. The research involves greater than minimal risk to subjects but no more than a minor increase over minimal risk.

The following benefit designations are used:

1. The research involves no prospect of direct benefit to individual subjects, or
2. The research involves the prospect of direct benefit to individual subjects

7.6 PERIOD OF APPROVAL

7.6.1 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 4.4.4B7h).

7.6.2 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.

7.7 INDEPENDENT VERIFICATION THAT NO MATERIAL CHANGES HAVE OCCURRED

7.7.1 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.

7.7.2 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.

7.7.3 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.

7.7.4 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.

7.7.5 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 and Incidents of Non-Compliance").

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
1. The proposed research design is scientifically sound & will not unnecessarily expose subjects to risk.	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?
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.	(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?
3. Risks to subjects are minimized.	Do data and safety monitoring plans make adequate provision for monitoring the data collected to ensure the safety of subjects.
4. Subject selection is equitable taking into account the purpose	a) Who is to be enrolled? Men? Women? Ethnic minorities? Children (rationale for

and setting of the research	inclusion/exclusion addressed)? Seriously-ill persons? Adults who may be unable to give consent? Healthy volunteers? b) Are these subjects appropriate for the protocol?
5. Additional safeguards are included for subjects likely to be vulnerable to coercion or undue influence.	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?
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.	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?
7. Subject privacy & data confidentiality are maximized.	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?
ADDITIONAL CONSIDERATIONS	
1. Ionizing radiation.	If ionizing radiation is used in this protocol is it medically indicated or for research use only?
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 AND FOR AMENDMENTS

<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 (46.111)?</p>
<p>2. Continuing review/amendment requirements</p>	<p>Have the relevant continuing review/amendment requirements as set forth in SOPs 9 and 10 been met?</p>
<p>3. Changes in previously approved research</p>	<p>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.)</p>
<p>4. Research risks</p>	<p>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?</p>
<p>5. Significant new findings</p>	<p>Are there any significant new findings that might affect the subjects' willingness to continue participation in research?</p>
<p>6. Protocol recruitment</p>	<p>Is the protocol meeting its recruitment goals?</p>
<p>7. Research progress and rationale for continuing the study</p>	<p>Is the research progressing as proposed/expected? Should the study continue?</p>
<p>8. Unanticipated problems (see Section III, below)</p>	<p>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</p>

	the summary of adverse events, protocol deviations, UPs or UADEs?
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SECTION III - 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

<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 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>a) Is this PD also a UP?</p> <p>b) Does this PD represent serious or continuing non-compliance? (see SOP 16A)</p> <p>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>

SECTION IV - 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).)

RISK LEVEL FOR ADULTS

Check appropriate risk category:

1. _____ Research not involving greater than minimal risk.*
2. _____ Research involving greater than minimal risk to subjects.*
3. _____ Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
4. _____ Research involving greater than minimal risk and no prospect of direct benefit to individual subjects.

***Note:** These risk analyses apply to competent adults (see SOP 14E “Research Involving Adults Who Are or May Be Unable to Consent” for adults who have surrogate decision-makers).

BENEFIT TO SUBJECTS

Note that the risk/benefit analysis for pregnant women, fetuses, or neonates may differ from the categories below, see 45 CFR 46.204 and .205.

A research benefit can be a health-related, psychosocial or other value to an individual research subjects. Money or other compensation for participation in research is not considered to be a benefit, but rather compensation for research-related inconveniences.

Check appropriate benefit category:

1. _____ No prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition;
2. _____ No prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge to further society's understanding of the disorder or condition under study;
3. _____ The research involves the prospect of direct benefit to individual subjects.

RISK/BENEFIT LEVEL FOR CHILDREN

(See SOP 14D "Research Involving Children")

Check appropriate risk category:

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)