HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL & IMPLEMENTATION

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

SOP Number: 8

SOP Title: PROCEDURES AND REQUIRED DOCUMENTATION FOR SUBMISSION AND INITIAL REVIEW OF PROTOCOLS

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

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8.1 PURPOSE

This SOP describes procedures and documents required for submission and initial review (IR) of a new protocol by an NIH Institutional Review Board (IRB).

8.2 POLICY

In fulfilling their mandate to protect the rights and safeguard the welfare of research subjects, a Principal Investigator's (PIs) submitted protocol and an NIH IRB's initial review of protocols must take into account federal regulatory requirements and those of the NIH Human Research Protection Program (HRPP).

8.3 REQUIRED ELEMENTS FOR NEW APPLICATIONS TO AN NIH IRB

A. The PI will complete and submit to the IRB an NIH Intramural Initial Clinical Protocol Application in the applicable IRB system, (PTMS or iRIS™) including any applicable supplements that are relevant to the protocol.

B. All Applications will be completed electronically, using either PTMS or iRIS™.

C. An NIH IRB administrative staff member will review the IR Application to assure its completeness before its review by the convened IRB.

8.3.1 DOCUMENTS TO BE ATTACHED TO THE ELECTRONIC APPLICATION

A. A written protocol that includes the sections listed in **8.4**, below, as applicable. The format of the written protocol may be determined by the individual IRBs, as long as all sections required by this SOP are present.

B. A written consent and, as applicable, assent document(s) using the NIH approved template if research is being conducted at the Clinical Center or at other non-CC NIH sites (e.g. NIA, NIDA, NIEHS, NIDDK-Arizona and NIAID Rocky Mountain Laboratories) Generally, for NIH intramural research conducted at non-NIH sites, NIH IRB-approved language is inserted into the local site templates. For other situations, for example when your subjects may be co-enrolled on the same protocol at both a NIH and non-NIH site, consult your IRB for guidance. For more information see, SOP 12 – Requirements for Informed Consent.

1. The consent and assent document(s) shall include the components listed in SOP 12 – Requirements for Informed Consent, and the requirements of SOP 14D – Research Involving Children, and, when the research is regulated by the FDA, the requirements of SOP 15 – Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications.

2. The consent document shall use specific headings and/or language required by the reviewing NIH IRB.

3. If there are multiple consent documents, each should be individually identified and labeled, e.g., “cohort 1”, “cohort 2”, “healthy volunteer.”

C. A copy of the Institute or Center (IC) scientific review (SR) and approval, or correspondence from the IC Clinical Director (CD) providing a justification for waiver of SR (when applicable).

D. The IC-approved Planned Enrollment or Cumulative Enrollment Report (NIH Application Supplements P and Q) as applicable. (For more information on NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, see **References** below and SOP 13 – Recruitment, Selection and Compensation of Research Subjects.)

E. For FDA-regulated research (if applicable): A copy of the Clinical Investigator's Brochure (IB), or appropriate alternative communication, along with any other required documents or correspondence, as applicable (see SOP 15 – Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications). If the PI has not submitted the IB or appropriate alternative information at the time of the initial application, the IRB must defer approval until the IB has been submitted and reviewed by the IRB.

F. Other required approvals, such as those of the Radiation Safety Committee, Recombinant DNA Advisory Committee (RAC), as applicable. If the PI has not submitted these other required approvals (as applicable) at the time of the initial application, approval must be contingent upon receipt of these approvals to the IRB Office, or deferred if additional IRB review is required.

G. The completed Clearance of NIH Investigator Personal Financial Holdings (PFH) form(s) (see SOP 21 – Conflict of Interest Requirements for Researchers and Research Staff). If a protocol is “covered” and the PI has not submitted the IC Deputy Ethics Counselor (DEC)-approved PFH at the time of the initial application, the IRB, if it were to otherwise approve the study, must delay approval until the final DEC Clearance has been submitted to the IRB Office (see SOP 21 – Conflict of Interest Requirements for Researchers and Research Staff).

8.4 REQUIRED PROTOCOL SECTIONS

A. Précis: In 3000 words or fewer, provide a description of the objectives, study population, design, and outcome parameters.

B. Table of Contents

C. Background

D. Study Objectives: including primary endpoint(s) and secondary endpoint(s), if applicable.

E. Study design and methods: including a description of the randomization procedure, if applicable.

F. Inclusion and Exclusion Criteria

G. Clinical and Laboratory Methods

H. Collection and Storage of Human Specimens or Data: All NIH IRB-approved research studies in which IRP researchers intend to collect and store human specimens or data must include:

1. A written description of the intended use of the samples.

2. How they will be stored.

3. How they will be labeled and/or tracked.

4. What will happen to the samples/specimens/data at the completion of the study, including the plan for data sharing if required by your IC Scientific Director and consistent with the NIH Genomic Data Sharing (GDS) and Human Data Sharing (HDS) policies, as applicable (see **References** below).

5. What circumstances would prompt the PI to report to the IRB loss or destruction of samples. For additional information, see SOP 5 – NIH Research Activities with Human Data/Specimens or contact OHSRP at 301-402-3444.

I. Statistical Analysis (as applicable)

1. For Phase III or IV clinical trials: The protocol should discuss the required sample size and how the trial will be analyzed statistically.

2. For Phase III trials, address the plan for valid design and analysis by sex/gender, race and ethnicity as required by the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research and SOP 13 – Recruitment, Selection and Compensation of Research Subjects, see **References** below.

J. Multiple-site studies: If the study involves subject enrollment at multiple sites, describe plans for ensuring appropriate IRB review and approval at each site, if a site will be relying upon the NIH IRB, list the names and roles of the investigators in the protocol (see SOP 20 – NIH HRPP Requirements for Collaborative Research and SOP 20A – Obtaining a Reliance (Authorization) Agreement at the NIH).

K. Human subjects protection plan should include at least:

1. The responsibilities of investigators.

2. The plan for obtaining informed consent, including procedures for telephone informed consent or other special circumstances, as applicable. If requesting waiver of informed consent or documentation of informed consent, provide a justification in the protocol (see SOP 12 – Requirements for Informed Consent).

3. The names of investigators or research staff who will obtain informed consent must be identified in the Intramural Initial Clinical Protocol Application and approved by the IRB.

4. For collaborative research involving a Reliance (authorization) agreement, NIH Federalwide Assurance (FWA) Coverage Agreement or an Individual Investigator Agreement (IIA), include the names and roles of NIH and non-NIH investigators engaged in human subjects research (HSR) in the protocol for approval by the IRB, (see SOP 20 – NIH HRPP Requirements for Collaborative Research, SOP 20A – Obtaining a Reliance (Authorization) Agreement at the NIH and SOP 20D – Collaborations Involving Non-NIH Employees Working on NIH Protocols).

5. Rationale for subject selection based on the equitable distribution of subjects, and the setting in which the research will take place. Additionally the protocol should include the scientific and ethical basis for the inclusion or exclusion of individuals on the basis of sex/gender, race, ethnicity and age (in particular, children) per the requirements specified by the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research, the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects, and SOP 13 - Recruitment, Selection and Compensation of Research Subjects, see **References** below.

6. Recruitment plan, including recruitment materials, advertisements, etc.

7. Rationale for involvement of vulnerable populations.

8. When discussing the research involvement of vulnerable subjects, include the appropriate requirements of:

    a. SOP 14A – Research Involving Vulnerable Subjects (General Considerations)

    b. SOP 14B – Research Involving Pregnant Women, Human Fetuses and Neonates

    c. SOP 14C – Research Involving Prisoners

    d. SOP 14D – Research Involving Children

    e. SOP 14E – Research Involving Adults Who Are or May be Unable to Consent

    f. SOP 14F – Research Involving NIH Staff as Subjects

9. Justification for exclusion of vulnerable populations

10. Evaluation of Risks/Discomforts and Benefits ratio: Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be expected to result.

    a. Describe the potential benefits to subjects or to others that may reasonably be expected from the research.

    b. Describe any potential risks -- physical, psychological, social, legal, or other -- and assess their likelihood and seriousness.

    c. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.

    d. Describe the procedures for protecting against or minimizing any potential risks, such as violations of confidentiality, and assess their likely effectiveness.

    e. Where appropriate, discuss provisions for ensuring that necessary medical or professional intervention is available in the case of adverse events to the subjects.

L. Protection of Participants' Privacy and Confidentiality: Describe how privacy and confidentiality will be protected. See SOP 18 – Privacy and Confidentiality.

M. Study Agents/Interventions: Describe the research drugs/devices or interventions to be used.

N. Plan for reporting unanticipated problems (UPs) and adverse events (AEs): This must be consistent with the requirements of SOP 16 – Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations.

O. If requesting the a waiver of reporting for anticipated PDs, expected non-UP AEs, or deaths, provide the justification in the protocol (see SOP 16 – Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations).

P. Data Safety and Monitoring Plan: This must be consistent with the requirements of SOP 17 – Data and Safety Monitoring.

Q. Clinical Monitoring Plan (if applicable): This must be consistent with the requirements of SOP 23 – Quality Management System for the NIH HRPP.

R. Data/Records Management: Describe how the research data will be managed and the safeguards in place to ensure confidentiality; see SOP 11A – Study Closure and SOP 18 – Privacy and Confidentiality for more information about records management.

S. Compensation: Describe the rationale for and amount of any proposed compensation consistent with SOP 13 – Recruitment, Selection and Compensation of Research Subjects.

T. Scientific references

U. Appendices (if applicable)

8.5 INITIAL IRB REVIEW OF PROTOCOLS

A. The IRB will conduct its initial review consistent with the requirements in SOP 7 – Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards, SOP 7A – Requirements for Expedited Review of Research by NIH Institutional Review Boards.

B. IRB minutes and records related to its initial review will be consistent with the requirements of SOP 4 – Human Research Protection Program (HRPP) Documentation and Records.

8.6 OFFICE OF PROTOCOL SERVICES (OPS) ACTIONS ON INITIAL REVIEW PACKAGES

8.6.1 SUBMISSION TO AND PROCESSING BY OPS OF IRB-APPROVED PROTOCOLS

When IRB and other required documentation and approvals are complete (see **8.3.1** above) including the IRB-approved, formatted informed consent(s), the protocol package is sent to OPS electronically. The appropriate steps are as follow:

A. Required data are extracted from the IRB-approved protocol and stored in the NIH Intramural Research Program data repository.

B. The completed package is forwarded to the Director, Clinical Center (CC) for Patient Safety/Resource review and signature when research is conducted at the NIH Clinical Center, or the Deputy Director for Intramural Clinical Research (DDICR) when the research is not conducted at the NIH Clinical Center.

C. Upon receipt of the signed protocol from the Director, CC, or from the DDICR, a protocol number is assigned, and for research conducted at the NIH CC, consent documents are posted to the intranet, and data elements are further transmitted as necessary (e.g., to the CC Clinical Research Information System (CRIS) and Clinicaltrials.gov).

D. OPS provides the PI and IRB a copy of the protocol signed by the Director, CC, or from the DDICR and the consent/assent document(s), which includes the CC watermark for studies conducted at the CC.

E. OPS staff will review the IRB-approved protocol package and identify missing or incomplete information. Depending on the extent of the information that needs to be resolved, the action may be returned to the IRB administrative staff for resolution; which may further require IRB staff to work with the PI to resolve the matter. Further action on the package will be placed on hold until the required information is received by OPS.

8.7 WHEN RESEARCH MAY BEGIN

Research may begin after completion of all steps in **8.6.1** above.

REFERENCES

A. NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October, 2001: http://nih-extramural-intranet.od.nih.gov/d/nih/topics/inclusionwo_main.htm

B. NIH Policy and Guidelines on the Inclusion of Children as Participants In Research Involving Human Subjects: http://nih-extramural-intranet.od.nih.gov/d/nih/policies/children.htm

C. NIH Genomic Data Sharing Policy:

D. NIH Human Data Sharing Policy