IRB HANDBOOK

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HOW TO USE THIS HANDBOOK

This handbook focuses on IRB responsibilities and provides IRB members and staff, and investigators and research staff information needed to comply with NIH Human Research Protection Program (HRPP) policies and human subjects protections regulations.

The language in this handbook was excerpted from the NIH HRPP Standard Operating Procedures and policies (SOPs). This handbook does NOT encompass all of the SOPs and should not be used as a replacement for NIH policies. For more complete information about these SOPs review the primary documentation at: http://ohsr.od.nih.gov/OHSR/pnppublic.php.

Chapters 1 – 7 cover IRB member and IRB Chair-specific requirements for NIH IRBs; Chapter 8 details responsibilities of the IRB Staff.

CHAPTER 1: THE NIH HUMAN RESEARCH PROTECTION PROGRAM (HRPP)

SOP 1 – HSR and the NIH IRB System

Version 4, 2-29-2016

1.2 Policy

NIH IRBs will review research involving human subjects in accordance with the U.S. Department of Health and Human Services (DHHS) regulations at 45 CFR 46 ("Common Rule") and the relevant NIH SOPs. This policy addresses human subjects research that is reviewed by IRBs. Research, that is exempt, or otherwise excluded, from IRB review under 45 CFR 46, is covered in SOP 5 and SOP 6.

1.9 Jurisdiction of Each IRB

Institutes with designated IRBs (single-institute IRBs - see **1.12**, below) generally review protocols from their own investigators. There are, however, exceptions to this rule, as follows:

A. **PIs from other Institutes:** When the PI of a research protocol is an employee of an NIH Institute/ Center (IC) that is not assigned to an IRB in **1.7**, above, (see **Appendix 1**, List of NIH Components Not Assigned to an IRB in SOP 1), that protocol will be reviewed by the IRB whose expertise is most closely related to the protocol's research topic. The PI initially contacts the administrative staff of the IRB that appears most appropriate. The appropriateness of that protocol for review is

determined by the IRB's Chair. If there is disagreement over the assignment of the protocol, the OHSRP Director will make the final decision. 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, except for the situations outlined below (see **1.9.B-E**).

B. **PI transfers or is detailed to another Institute:** If a PI transfers or is detailed to another Institute, the appropriateness of transferring the study to another NIH IRB will be evaluated. In the event that there is any uncertainty or dispute regarding which NIH IRB should review a protocol, the Deputy Director for Intramural Research (DDIR) will make the final determination, or delegate that authority to OHSRP. If a protocol is transferred between NIH IRBs, please refer to SOP 27 for further guidance.

C. IC Directors, Scientific Directors, and Clinical Directors:
   1. The NIH *Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Human Subjects Research* (see SOP 21) states that Institute Directors and Institute Scientific Directors must have their protocols reviewed by an IRB not affiliated with their Institute when they are a PI or an AI on a protocol. The DDIR may waive this requirement.

   2. IRBs have the prerogative to review the protocols of their Institute's Clinical Director (CD) or refer them to another Institute's IRB. IRBs reviewing protocols in which their CD is the PI must have a majority of members who are not employed by the CD's Institute, otherwise any alternative plan must have prior approval by the DDIR.

D. **Other Circumstances:** Circumstances may justify having a protocol reviewed by an NIH IRB other than the one to which it would be assigned under the rules above. The DDIR has the authority to determine which IRB will have jurisdiction over such a protocol or may delegate the authority to OHSRP.

1.10 Authority of the IRBs

A. Each NIH IRB has the regulatory authority to:

   1. Approve, modify or disapprove research (45 CFR 46.109(a))

2. Suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. (45 CFR 46.113)

3. Observe, or have a third party observe, the consent process (45 CFR 46.109(e))

B. The IRBs also have authorities associated with:

1. The consent process (45 CFR 46.109(b)-(c), 45 CFR 46.116).

2. Continuing review (45 CFR 46.109(e)).

3. Applicable authorities per the FDA.

1.11 Frequency of Meetings

Each of the NIH IRBs has regularly scheduled meetings. If necessary, IRBs may convene special meetings.

1.13 Review of IRBs' Performance

IRBs' performance is reviewed and evaluated as described in SOP 26.

1.14 Independence of the IRBs

A. In exercising the authority provided to them under **1.9**, above, the NIH IRBs will at all times maintain their independence. The DDIR, who serves as the Institutional Official, will oversee the NIH Human Research Protection Program (HRPP) in a manner that assures that the IRBs can exercise their authority independently.

B. The SDs' and CDs' administrative responsibilities for providing resources for IRBs and nominating potential IRB members do not include authority to unduly influence IRB decisions. IC Directors, SDs and CDs must respect IRB decisions.

C. An IRB member who is concerned about undue influence or inappropriate communications from any source should first report the occurrence to the Chair of that IRB, who will attempt to mediate or resolve the concern, in consultation with the applicable CD, OHSRP, or other NIH officials, as necessary or appropriate.

E. Any individual who believes that inappropriate communications or undue influence have not been appropriately resolved in a timely manner, should report the matter to OHSRP or the DDIR.

CHAPTER 2: IRB RESPONSIBILITIES

SOP 2 – IRB Membership and Structure

Version 2, 2-24-2016

2.2 Policy

The NIH Human Research Protection Program (HRPP) ensures that its IRBs are constituted consistent with federal regulatory requirements. It has procedures in place for (1) appointing and reappointing members; (2) maintaining current IRB rosters; (3) communicating members' responsibilities to them; (4) removing members for cause, and (5) clarifying their legal liability.

2.3 Requirements for IRB Membership

2.3.1 Regulatory Requirements

Consistent with the requirements of 45 CFR 46.107 and 21 CFR 56.107, the IRB must:

A. Be composed of at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution;

B. Be sufficiently qualified through the experience and expertise of its members and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects;

C. Have a membership not consisting entirely of men or entirely of women, so long as no member is chosen on the basis of gender;

D. Have at least one member whose primary concerns are in scientific areas;

E. Have at least one member whose primary concerns are in non-scientific areas;

F. Have at least one member who is not otherwise affiliated with the NIH and who is not part of the immediate family of a person who is affiliated with the NIH; and

G. If the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more members who have knowledge about and experience with these subjects.

One person may fulfill both the requirements of item E and those of item F.

2.3.2 IRB Member Area of Expertise and Affiliation

A. In determining member expertise, affiliation and status as primary or alternate member, the following criteria apply:

1. **Affiliated member:** An NIH employee (or a member of that person's immediate family) is considered affiliated. Affiliated members also include, but are not limited to, individuals who are at or involved with NIH as: part-time employees; current students; trainees; members of any panel or board; paid or unpaid consultants; healthcare providers holding credentials to practice at the NIH; guest researchers; and volunteers.

2. **Unaffiliated member:** If an individual has no affiliation with the NIH, other than as an IRB member, then s/he is considered unaffiliated. Unaffiliated members may include people whose only association with the NIH is that of a research participant, or former student, trainee, contractor or employee. Paying unaffiliated members for their services would not make the member "otherwise affiliated", or cause the member to have a conflicting interest.

   a. **Note:** An IRB member will only be considered "unaffiliated" when he/she has properly completed and submitted to the designated IRB a "Statement of Status as Unaffiliated Member of an NIH IRB" (see **Appendix A** in SOP 2). The designated IRB will make the statement available to the Office of Human Subjects Research Protections (OHSRP). Concerns about affiliation will be submitted to OHSRP, which will make the final determination regarding the member's affiliation status.

3. **Members whose primary interests are in scientific areas:** A member whose highest level of education/training and/or occupation is from a scientific discipline or profession, e.g. the physical sciences, biomedical sciences, social/behavioral

sciences, or mathematical sciences and who would be inclined to view scientific activities from these standpoints. The IRB must have members with sufficient knowledge of the specific scientific discipline(s) relevant to the research that it reviews.

4. **Member whose primary concerns are in non-scientific areas:** A member whose education, training, background, and occupation would incline him/her to view research activities from a standpoint other than any biomedical or behavioral scientific discipline should be considered a non-scientist.

5. **Alternate members:** (see **2.3.4** below) are members who may substitute for a primary IRB member or a category of member (e.g., physician or nurse). Each alternate IRB member has experience, expertise, background, professional competence and knowledge comparable to that of the primary IRB member(s) whom the alternate would replace.

B. The determination of whether the nominated IRB member's primary concerns are in scientific or non-scientific areas, will be made by the designated IRB at the time when members are nominated for appointment. The IRB will base this designation on a review of the nominee's *curriculum vitae* and IRB member survey (see **2.4.2** and **2.5** below). When there are concerns about this designation, OHSRP will make the final determination of whether a nominated IRB members' primary concerns fall into scientific or non-scientific areas consistent with criteria provided in **2.3.1** above.

C. Consistent with Office for Human Research Protections (OHRP) guidance, IRB members can only be appointed as either regular (primary) or alternate members. There is no category of non-voting member of the IRB.

D. It is the responsibility of the Clinical Director (CD), in conjunction with the IRB Chair, to ensure that the IRB's overall composition meets regulatory and NIH requirements. OHSRP will review IRB composition annually to ensure compliance (see **2.4.2** and **2.5** below).

E. The IRB Chair shall at least annually notify OHSRP in writing whether the IRB regularly reviews research that includes any of the categories of vulnerable individuals mentioned in **2.3.1.G** above.

2.3.3 Additional NIH Membership Requirements

A. Consistent with NIH Manual Chapter 3014, NIH has the following additional IRB membership requirements:

1. A scientific or professional staff member not affiliated with the IRB's Institute.

2. A member with expertise in statistics or an epidemiologist.

3. A member who is either a pharmacist or pharmacologist, and

4. An ethicist or individual who has expertise in the ethics of human subjects protection.

   A. The inclusion of an ethicist is desirable, where practicable. Individual IRBs have the discretion to include one as a primary member or consultant, depending on the existing composition of the board, as well as the nature of the research being reviewed.

   B. **Note:** For several of the intramural IRBs, a member of the senior staff of the Clinical Center (CC) Department of Clinical Bioethics participates as a primary member. For other NIH IRBs, the CC Department of Clinical Bioethics has recommended, as possible members, individuals who have knowledge and experience with research ethics. An IRB may also independently nominate an ethicist for its committee.

5. **Non–scientist members:** The U.S. Department of Health and Human Services (DHHS) human subjects regulations require that each IRB shall include at least one member whose primary concerns are in non-scientific areas. However, NIH strives to maintain a 20% ratio of non-scientist members on each IRB.

6. At least one member of the IRB must represent the perspective of research participants.

7. NIH IRB administrative staff may not be members of the IRB.

8. Institute and Center (IC) Directors, Scientific Directors (SDs), CDs and Office of Tech Transfer staff may not be members of the IRB.

B. Based on a written request and justification by the appropriate Institute CD, OHSRP can determine that an NIH IRB need not comply with the additional NIH policy requirements set forth in **2.3.3.A.** for a biostatistician, pharmacist, or bioethicist

member. This does not preclude the regulatory requirement for a non-scientist at each IRB meeting to establish a quorum.

2.3.4 Additional Requirements for Alternate Members

A. **Appointment process:** The appointment process is the same as for primary members of the IRB (see **2.5** below). Alternates' names are included in the IRB's official membership roster (see **Appendix H** in SOP 2) with the designation that they are alternates, together with the name(s) of the IRB member or category of members for whom they are an alternate.

B. **Assignment of alternates:** An alternate member may be assigned as a substitute for one or more named primary members or for a category of members. Alternates must have qualifications similar to those of the member(s) for whom they are allowed to be a substitute. Alternate members receive agenda packages for all IRB meetings and are encouraged to attend as many meetings as possible, even when not required to be present to act as an IRB member.

C. **Alternate members and the quorum:** When an alternate member substitutes for a regular member, the alternate member's vote counts towards the quorum in the same way as the regular member's vote.

D. Voting by alternate members:

1. Alternate members vote on protocols or other matters at convened meetings only when one of the primary members for whom they are an alternate is not participating in the vote (e.g., because that member is absent or has a conflict of interest). They should only participate when they have, prior to the meeting, adequately reviewed the materials distributed with regard to the protocol or other matters on which they would be voting. The IRB minutes should document the alternate member's votes.

2. A designated alternate IRB member may substitute for the primary IRB member for an entire meeting or at any time during a meeting. Substitution during a meeting commonly occurs when the primary member is (a) absent from the room for part of the meeting, or (b) recused from review of certain research protocols because the primary IRB member has a conflicting interest with respect to a specific research protocol. Whenever this occurs, the minutes of the IRB meeting should indicate clearly that the alternate IRB member has replaced the designated primary IRB member.

2.5 Appointment and Reappointment Procedures and Terms of Service

2.5.1 Procedures for Initial Appointment to the IRB

A. **Identifying members:** The Institute CD or CDs (in the case of multi-Institute IRBs), the IRB Chair, and, at the discretion of each IC, the SD, recommend the appointment of the IRB Chair, the IRB Vice Chair and IRB members (including alternate members). In making such recommendations, consideration will be given to the requirements above for IRB membership and representation. The designated IRB will provide the prospective nominee with the IRB Member Survey to ensure that they satisfy the IRB's composition and representative capacity requirements.

a. Nominees and their supervisors should agree to the nomination.

b. The Director, SD and CD of any IC may not serve as a member, IRB Chair or Vice Chair of any NIH IRB.

A. **Specific considerations for nomination of Chair and Vice Chairs:** Nominees for IRB Chair and Vice Chair should have experience in human subjects research, which could include previous experience serving on an IRB; be knowledgeable about the scientific mission and clinical program of the particular Institute or Institutes for which the IRB serves as the primary IRB, and be familiar with the federal regulations for the protection of human subjects (45 CFR 46 and 21 CFR 50 and 56) and the ethical basis for the regulations (The Belmont Report).

B. **Completion of required training:** Before beginning service as a member of the IRB, all nominees, including those for Chair and Vice Chair, must complete the training requirements that are specified in SOP 25. Designated IRBs should notify nominees of their training requirements and ensure that all training requirements are met. IRBs are reminded to monitor continued compliance with training requirements for all IRB members.

2.5.2 Reappointment Procedures

C. Expiration of Terms: After the expiration of the term of an appointment, an individual is considered to be inactive as a member of the IRB and may not participate in IRB meetings (except as a consultant, according to the requirements at **2.11**, below) until the reappointment letter from OHSRP has been signed.

2.5.3 Terms of Service

A. Unless reappointed, Chairs, Vice Chairs and members rotate off the Board when their terms expire and have not been renewed, when members tender their resignations, or when members are removed for cause.

a. Members who complete their term of service and are not reappointed will receive a Thank You letter from the DDIR. The designated IRB office will prepare the letter and submit it to the DDIR for signature. The DDIR will return the signed letter to the designated IRB. The signed letter will be sent to the member via the designated IRB and will be copied to the CD, SD, IRB Chair and OHSRP, (see **Appendix G** in SOP 2).

B. IRB Chairs, Vice Chairs and members may be reappointed in conformity with the rules stated in **2.5.2** above. There is no limit on the total number of years members may serve as a result of being reappointed multiple times, unless Institute management wishes to impose a limit.

C. Chairs and Vice Chairs may serve as regular IRB members on the same IRB or another NIH IRB after their terms as Chair and Vice Chair are completed.

2.5.4 Removal for Cause of a Member

A. **Justification for Removal:** To remove a member of an IRB, including the Chair or Vice Chair, before the end of that person's appointed term, just cause must be shown of that person's inability to meet his/her responsibilities as an IRB member, such as failure to attend meetings regularly; failure to follow applicable laws, regulations and policies; mismanagement; misconduct, or an unresolved conflict of interest for which recusal is insufficient.

B. **Procedures for Removal:** The Institute CD, after consultation with the Institute SD and the Chair (if the Chair is not the member in question) should prepare a written memorandum to the DDIR through the Director, OHSRP, with the reasons for recommending premature termination of membership. The DDIR makes the final decision on termination and sends a termination letter to the member if s/he concurs with the recommendation for removal from the IRB.

C. Termination letters are copied to the CD, IRB Chair, OHSRP, and the designated IRB administrative office.

D. **Reconsideration for Terminated Members:** Terminated members or those who are about to be terminated may ask the DDIR for reconsideration.

2.7 Responsibilities of the Vice Chair

Each IRB is required to have a Vice Chair. The Vice Chair vote counts towards the quorum, unless recused, and they either vote or abstain from voting on all actions for which votes are taken. Vice Chairs will recuse themselves, as appropriate, when conflicts of interest exist. The Vice Chair, in the Chair's absence, exerts all authorities ordinarily vested in the Chair (see **2.6** above).

2.8 Responsibilities of IRB Members

Members of the IRB (including the Chair, Vice Chair, and alternate members) must:

A. In convened meetings, apply the NIH IRB Protocol Review Standards or an appropriate reviewer tool when reviewing initial protocols (see SOP 7).

B. Attend IRB meetings regularly (at least 75% of meetings per year) and in those instances in which they are unable to attend a meeting, provide the longest possible notice of their inability to attend.

C. Be well prepared to discuss each meeting agenda item as a result of having spent sufficient time prior to the meeting reviewing the materials distributed for that meeting, and reviewing the minutes of previous meetings for accuracy.

D. Complete the IRB Member Survey when it is issued on an annual basis.

E. Maintain the confidentiality of IRB discussions, the votes of individual members, and the protocols and related materials, including any proprietary information (see SOP 7).

F. Participate in required training and continuing education opportunities, or IRB retreats (see SOP 25), and

G. Inform the IRB immediately if their status changes in a way that might impact their membership (such as a new affiliation with the NIH for a member who was previously considered unaffiliated).

2.9 Compensation of IRB Members

Annually, each IRB will provide information to OHSRP in writing about if, and how, IRB members, including the Chair and Vice Chair, are compensated for their IRB service.

2.10 Liability Coverage for IRB Members Affiliated with NIH through Any of the Following Four Categories: Special Government Employees (SGEs), Special Volunteer, Contractor, Or Employee

2.10.1 Background

Liability coverage for IRB members differs depending on whether they are federal employees (either full-time or as a special government employee), or non-Federal employees who serve on the IRB without compensation (i.e., a volunteer member) or who are compensated.

2.10.2 NIH and Other Federal Employees

The Federal Tort Claims Act (FTCA) (28 U.S.C. 2671 et seq.) generally covers Federal employees in litigation when there are allegations of negligence that occurred within the scope of their employment.

A. NIH and other federal employees, whose IRB service is considered part of their official duties, are covered by the FTCA. Employees should have documentation in their personnel files that their IRB service is an official duty.

B. An individual who is not presently an employee may be appointed as a special government employee (SGE) specifically for service as an IRB member. The individual must complete various personnel forms, including a financial disclosure form and agree to abide by applicable Federal ethics requirements.

2.10.3 Volunteer Members of the IRB

It is considered that volunteers may be eligible under the FTCA for coverage from personal liability for damages or injuries that arise from actions occurring within the scope of their federal assignment as NIH IRB members and while under the direct supervision of a federal employee. However, the ultimate decision on issues of liability and coverage depends on the circumstances of each situation as it does for federal employees and is made by the U.S. Department of Justice. These individuals must obtain a Special Volunteer appointment at the NIH.

2.10.4 Compensated IRB Members Who Are Not Federal Employees

Non-Federal employees may receive compensation for services as contractors. They are not covered by FTCA but may purchase private liability coverage for IRB services. The cost of such coverage may be reimbursed under their contract with NIH.

2.11 Selection and Use of Consultants for Review

2.11.1 Use of Consultants

Consistent with requirements set forth at 45 CFR 45.117(f), an NIH IRB may choose to invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. This may include experts in scientific aspects of the research or related to human subjects protections.

2.11.2 Choosing Consultants

The IRB Chair, in cooperation with the CD(s), will identify appropriate experts (based on their *curriculum vitae, c*urrent work in the relevant scientific discipline, etc.). Consultants may be drawn from scientific or other NIH staff, as well as from outside the NIH.

2.11.3 Consultants' Conflict of Interest

Consultants are subject to the same NIH conflict of interest rules as IRB members and are required to self-identify if they have a conflict of interest (see SOP 21).

2.11.4 Provision of Consultant Advice

A. The IRB administrative office ensures that the consultant understands his/her confidentiality obligations and receives a copy of the proposed protocol and any other supporting documentation in a timely manner.

B. Consultants may attend IRB meetings in person or submit a written report to the Board. Consultants may attend the convened IRB meeting; question the protocol's PI during the PI's presentation; provide an oral critique of the protocol after the PI has left the room, and participate in discussions of the protocol with other IRB members.

C. Consultants do not vote and are excused from the meeting prior to the vote. Their presence is noted in the IRB meeting minutes.

2.12 Use of Subcommittees for Review

Subcommittees of the IRB may be created as needed at the discretion of the Chair. They may be constituted to consider a specific issue or issues, or to review and approve a protocol under an expedited review process (SOP 7A) or to review an investigator's response to stipulations when this authority has been specifically delegated to them by

the IRB Chair or convened IRB. If a HRPP SOP requires that an issue be reviewed at a convened meeting of an IRB, then review by a subcommittee can never serve as a substitute for that convened IRB review. Subcommittee actions are reported to the full Board at the next convened meeting.

2.13 Evaluation of IRB Members

IRB members will be evaluated at least annually to assess their knowledge of ethical principles and basic regulatory requirements, attendance at, preparedness for and participation in meetings. The evaluation of the IRB Chair will be performed by the DDIR or OHSRP designee. IRB Chairs will evaluate the members of their designated IRB. For further guidance, see SOP 26.

2.14 Training, Education and Professional Development for IRB Members

Incoming IRB members must complete all required training before they can commence their appointment. Reappointed IRB members must be compliant with all HRPP training requirements before resuming their position on the board. IRB Chairs may require IRB members to take additional training based on the type of research reviewed by the IRB. Additionally, IRB members should attend retreats and educational opportunities as provided by the IRB to which they belong. For further guidance, see SOP 25.

SOP 7 – Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)
Version 3, 8-7-2015

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).

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

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.

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 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** in SOP 7) as a tool to assist in 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.

7.8 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). 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).

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).

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).

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).

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 and SOP 14A).

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.

The NIH IRB Protocol Review Standards (**Appendix A** in SOP 7) 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** in SOP 7 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).

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).

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 and SOP 16A.

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).

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).

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).

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).

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 and SOP 16A). 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, 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.

SOP 7A – Requirements for Expedited Review of Research by Institutional Review Boards
Version 3, 8-4-2015

7A.2 Policy

Research activities that satisfy 45 CFR 46.110 and 21 CFR 56.110 (when applicable), may be reviewed through the expedited review procedure. Like review by the convened IRB, expedited review must fulfill all the requirements of review found at 45 CFR 46.111 and subparts B, C, and D, if applicable.

7A.5 Procedures for Review of Research Activities by the Expedited Process

A. **Pre-review of Research Activities for Expedited Review:** The IRB staff, in consultation with the IRB Chair or designee, pre-reviews all submissions for expedited review, including applications for expedited initial review, expedited continuing review, expedited closure of protocols, and expedited amendments for minor changes to previously approved research. The determination of whether an item is eligible for consideration under the expedited review procedure is made by the IRB Chair or designee. The decision whether to expedite eligible items or to send them for full Board review is at the discretion of the IRB Chair or designee.

B. Selection of Reviewers for Research Activities Eligible for Expedited Review:

1. The IRB Chair, or one or more experienced IRB members designated by the Chair, may review and approve research that meets criteria for expedited review.

2. An experienced IRB member is defined as a regular or alternate member who knows the expedited review categories, and, in the judgment of the Chair, possesses the expertise needed to review the proposed research.

C. Responsibilities of Reviewers

1. Reviewers may obtain additional consultation.

2. Reviewers may approve submissions unconditionally or approve with stipulations but may not disapprove research.

   a. If the reviewer determines that the research is not eligible for expedited review, or even if eligible for approval by expedited review but should still be reviewed by the convened IRB, this recommendation will be forwarded to the IRB Chair for non-expedited review by the convened IRB.

   b. If the reviewer determines expedited review is appropriate for the research, the reviewer will determine a review interval for approved expedited research not less than once per year (see SOP 7).

   c. Any stipulations that must be met prior to final approval of expedited research are sent to the investigator by mail or email and documented in the IRB file. Final approval is provided by the IRB Chair or designee when the response to stipulations has been submitted and approved by the designated reviewer.

7A.6 Procedures for Initial Review by the Expedited Process

Only complete submissions that meet the requirements specified in SOP 8 will be accepted for expedited review. The reviewer(s) will have access to all of the materials submitted for review. Research materials submitted for review must include sufficient

detail for the reviewer(s) to determine: (i) that the study qualifies for review by an expedited process, and (ii) that the study meets the approval criteria that are specified in SOP 7. In conducting such a review, the reviewers will document the IRB reviewer's determination in the IRB system, which includes a reviewer checklist **(Appendix A** in SOP 7A**)**.

7A.7 Procedures and Criteria for Continuing Review by the Expedited Process

The procedures for expedited review for continuing research activities are the same as the procedures for continuing review by the convened IRB as described in SOP 9 except that expedited review must be documented in the IRB system consistent with the requirements specified in Appendix A in SOP 7A and the review is to occur consistent with the expedited process explained in **7A.5.B and C**.

A. Continuing Review of a Research Activity Initially Approved by an Expedited Review:

   A research activity that is initially approved by expedited review may use an expedited review procedure for continuing review. For this to occur, the research activity must still qualify for expedited review as described in **7A.3** above. If it does not qualify, continuing review at a convened IRB meeting must take place.

B. Continuing Review of Research Activities Previously Approved by the Convened IRB:

   Continuing review for research activities previously approved by the convened IRB may be conducted through expedited review provided they meet the criteria for approval as described by expedited review categories (8) and (9) (**Appendix B** in SOP 7A) as permitted by 45 CFR 46.110. IRBs are reminded that expedited review usually is not appropriate at the time of continuing review if the research required review by the convened IRB at the time of initial review.

7A.8 Procedures and Criteria for Expedited Review of Amendments that Constitute a Minor Change

A. **Procedures:** SOP 10 contains some requirements for general amendments and expedited review of amendments. Expedited review of amendments that constitute a minor change have additional criteria and NIH policy requires that the reviewer document the IRB reviewer's determination in the IRB system consistent with the requirements specified in **Appendix A** in SOP 7A.

B. **Criteria:** Criteria for Determination of Eligibility for Expedited Review of Amendments:

   1. Amendments to research previously approved by expedited review may be reviewed through the expedited process as long as the amendment does not make the study ineligible for expedited review.

2. Expedited review can be used for amendments making minor changes to previously approved research, whether previously approved via expedited review or not. A minor change is one which, in the judgment of the reviewer, makes no substantial alteration in:

   a. The risk-benefit profile of the study.

   b. The presumed willingness of current subjects to remain in the study.

   c. The scientific validity of the research design or methodology. (Note: adding procedures that are not eligible for expedited review would not be considered a minor change).

   d. The number of subjects enrolled in the research.

   e. The qualifications of the research team. (**Note:** the addition or deletion of investigators usually is a minor change; however, a change in PI may not qualify as a minor change).

   f. The facilities available to support safe conduct of the research.

7A.9 Reporting and Documenting IRB Actions regarding Expedited Review

1. The reviewer of expedited actions documents determinations in the IRB system per **Appendix A** in SOP 7A, including the specific expeditable category or categories relevant to the action.

2. IRB members are provided with a written list of all actions approved by the expedited procedure in the next meeting agenda. IRB members may request additional information.

3. The IRB will provide the PI with the outcome of expedited review.

4. Expedited review actions announced at a convened IRB meeting are listed in that meeting's IRB minutes.

5. The expedited actions are entered and tracked in the IRB and Office of Protocol Services (OPS) databases in the same way as non-expedited actions.

SOP 8 – Procedures and Required Documentation for Submission and Initial Review of Protocols
Version 4, 1-12-2016

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).

8.5 Initial IRB Review of Protocols

A. The IRB will conduct its initial review consistent with the requirements in SOP 7 and SOP 7A.

B. IRB minutes and records related to its initial review will be consistent with the requirements of SOP 4.

SOP 9 – Continuing Review by the Convened IRB
Version 3, 3-3-2016

9.2 Policy

Consistent with 45 CFR 46.109(e), and OHRP "Guidance on IRB Continuing Review of Research", dated November 10, 2010, (see **References** in SOP 9), NIH IRBs shall conduct CR of human subjects research at intervals appropriate to the degree of risk, but not less than once per year.

When conducting CR, the IRB should start with the working presumption that the research, as previously approved, does satisfy all of the regulatory criteria. The IRB should focus on whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB's prior determinations, particularly with respect to the IRB's prior evaluation of the potential benefits or risks to the subjects. The IRB also should assess whether there is any new information that would necessitate revision of the protocol and/or the informed consent document.

9.3 Regulatory Requirements for CR

A. NIH IRBs conduct CR for each research study to ensure the continued protection of the rights and welfare of research subjects in accordance with 45 CFR 46.109(e) and, as applicable, 21 CFR 56.109(e). The IRB applies the same criteria for approval at the time of CR as it does for Initial Review (IR) of studies (see 45 CFR 46.111, SOP 7, and 21 CFR 56.111). Note that the IRB's CR for a protocol that's remaining research activities include data analysis only may be performed as expedited review using an

abbreviated process (**see 9.6.1 below**).

B. CR occurs at intervals appropriate to the degree of risk, but not less frequently than once a year. The IRB must set the frequency for CR based on its analysis of risk at the time of initial (see SOP 7) and CR and may increase the frequency of review, i.e., if new information negatively impacts the risk/discomforts and benefits ratio, if the IRB is notified of a complaint or alleged non-compliance or for any other appropriate reason.

C. CR of research must be substantive and meaningful. At CR, the IRB will decide whether the research continues to meet the criteria for IRB approval as set forth in 45 CFR § 46.111.

D. NIH IRBs will review information provided by the Principal Investigator (PI) about the number and types of vulnerable subjects enrolled and determine whether the protections for vulnerable subjects continue to be adequate (see SOP 14A).

9.4 Research Studies Which Require CR

A. CR and re-approval of all non-exempt research studies, including those approved by expedited review (see SOP 7A), is required at least annually as long as the study remains active, e.g., human subjects are engaged. Active studies include all non-exempt IRB approved research when, for example:

1. Recruitment of subjects has not yet begun.

2. There is active recruitment and enrollment of subjects.

3. The study is no longer recruiting, but research remains active for long-term follow-up.

4. Subjects have completed all research-related activities and data analysis of private identifiable information is ongoing (see **9.6.1** below for a discussion regarding the expedited continuing review process for ongoing data analysis); or

5. Research is under suspension or administrative hold (e.g., recruitment or enrollment of subjects is suspended see SOP 11).

B. Federal regulations and NIH policy do not provide for exceptions to the requirement for CR; therefore, failure by the PI to ensure timely IRB review and approval is a

serious matter that could lead to suspension and possibly termination of the study (see **9.12** and **9.13** below and SOP 11) regarding what may occur when IRB approval expires. Continuing research activity on an expired study is considered non-compliant with HRPP policies and regulations and must be reported as described in SOP 16A.

9.5 Timing of the CR Submission

A. CR and approval must be completed by midnight on the date on which IRB approval of the research study would expire (the "expiration date"). See **9.10** below, for the explanation of how the expiration date is determined.

B. It is the PI's responsibility to ensure that the review and IRB re- approval of ongoing research is conducted before the expiration date.

C. As a courtesy, the IRB office sends at least two separate reminders to the PI of the expiration date.

9.6.1 Expedited Continuing Review Submission Requirements when the Protocol Activities Are Limited to Data Analysis Only

This section applies only to expedited CR submission requirements when protocol activities are limited to data analysis.

In its "Guidance on IRB Continuing Review of Research", OHRP notes that the process for CR of research under expedited review category 8(c) can be accomplished through a simple, abbreviated process.

Under expedited review category 8(c) (see **References** in SOP 9), an IRB may use an expedited review procedure to conduct CR when the only remaining human subjects research activity is the analysis of data that includes identifiable private information, and the IRB chair (or designee) determines that the research involves no more than minimal risk. This can be accomplished in a simple, abbreviated process provided that the CR submission to the IRB and must include statements that:

A. No subjects were enrolled during the previous twelve months

B. All subjects have completed all protocol visits or otherwise have withdrawn from the study

C. No new data are being collected

D. During the previous 12-month review period, there have been no adverse events, unanticipated problems, deviations, breaches of confidentiality, and no loss of specimens or data or other protocol-related problem that otherwise requires reporting to the IRB at the time of continuing review.

E. Any information in the literature, or evolved from similar research that might affect the IRB's analysis of risk/benefit for the protocol. If such information is obtained before the time of CR, it should be reported to the IRB at the time that it becomes known, and summarized at the time of CR.

F. The IRB may require additional information by stipulation.

9.7 Procedures for CR by The Convened IRB

A. An IRB staff member, or a designee, will review each IRB submission package to determine that each of the required items has been submitted.

B. NIH IRBs may elect to assign primary (and possibly secondary) reviewer(s) to conduct a preliminary review of the CR materials and present the findings at the convened IRB meeting (see SOP 7 for details). However, all IRB members should be provided with and are expected to review the materials described in **9.6** above prior to the convened IRB meeting. At the convened IRB meeting, the primary and, if applicable, the secondary reviewer leads the IRB through the criteria for approval, using the IRB's CR checklist, as applicable.

C. The complete IRB file for the particular protocol will be available to IRB members before, during, and after the IRB meeting.

D. IRB members or the primary and if applicable secondary reviewer, if applicable (see SOP 7), will:

1. Confirm that the current consent/assent is still accurate and complete.

2. Consider if new or additional risks have been identified (e.g. UPs) that would require changes to the research study protocol, consent form, review frequency, etc.

3. Consider if any new information may impact subjects' willingness to continue participation.

4. Review the Memorandum of Progress for the status of enrollment and retention of subjects to assess the consistency with the recruitment plan in the protocol (see SOP 13).

5. Verify that no material changes have been made since the previous IRB review or determine that independent verification is needed. In making this determination, the IRB takes into account the risk level of the research study; whether the PI has previously failed to comply with IRB requirements; when materials submitted for CR include unapproved modifications or inconsistent information, or when the IRB has been informed of non-compliance by other sources.

6. Determine if new NIH policies necessitate changes in the study and/or consent. Changes that do not impact subject safety or welfare may be stipulated for completion prior to the next CR or within a stipulated timeframe.

7. Determine that each of the elements of 45 CFR 46.111 is satisfied.

8. If applicable, determine that the requirements of Subpart B (Pregnant Women, Fetuses, Neonates), C (Prisoners), D (Children) are met.

E. Each study that is scheduled for CR at a convened meeting is discussed and voted upon at the meeting and documented in the IRB Minutes (e.g., see SOP 4, SOP 7 and SOP 2).

F. The IRB votes separately on new amendments that accompany CRs (see **9.6.B.8** above).

9.8 IRB Actions on CRS

The types of action possible at CR are the same as for IRs (see SOP 7).

9.9 Notifying the PI about IRB Actions

The IRB will notify the PI in writing of the IRB's determination see SOP 7).

The IRB communication to the PI will also indicate the next expiration date. The correspondence also reminds the investigator that changes in research activity may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to subjects.

9.10 Setting the CR (Expiration) Date

A. To determine the date of initial approval, see SOP 7.

B. To determine the date of CR:

1. Setting the date of the first CR:

   a. For a study approved at IR by the convened IRB without stipulations/conditions, the approval period starts on the date the convened IRB approved the research.

   b. For a study approved at IR with stipulations/conditions, the approval period starts on the date the Chair or designee approves and signs off on the stipulations/conditions.

   c. For a study initially approved by expedited review, the approval period begins on the date the IRB Chair or IRB member(s) designated by the Chair gave final approval to the study.

2. Setting the date of the second and subsequent CRs:

   a. **No Fixed Anniversary Date:** The date of the last IRB approval (with or without stipulations/conditions) determines the latest permissible date of the next CR (see Section 9.12, below), **OR**

   b. **Fixed Anniversary Date:** If the IRB conducts its CR and approves the study for a year-long time period and approves the study (with or without stipulations/conditions) within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.

   c. At the time of initial and CR, 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 (see SOP 7). The meeting minutes will reflect the IRB's determination regarding the frequency of review (see SOP 4).

9.12 Lapses and IRB Approvals with Stipulations

9.12.1 No Provision for a Grace Period

The regulations and NIH policy make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, CR and re-approval of research with or without stipulations/conditions must occur by midnight of the date when IRB approval expires. The IRB Chair and staff do not have the authority to extend the CR date of the research.

9.12.2 Lapse in IRB Approval

A lapse in IRB approval of research occurs when~~ever~~ an investigator has failed to provide continuing review information to the IRB or the IRB has not conducted a continuing review and re-approved the research - with or without stipulations/conditions - by the expiration date of IRB approval. For instance, if an IRB has conducted continuing review but tabled or deferred the research and the expiration date passes, the research has lapsed.

When a lapse occurs, research activities (including recruitment, enrollment, consent, interventions, interactions, data collection and data/sample analysis) must stop. However, the IRB has authority to allow continuation of research for some or all previously-enrolled subjects if the IRB finds that continuation is in the best interest of the subjects. For example, the IRB may find that research interventions hold prospect of direct benefit to subjects or, alternatively, withholding study interventions may pose increased risk for subjects. The IRB must document its approval for the continuation of research for these subjects.

9.12.3 IRB Approval with Stipulations

An IRB has authority to approve research with stipulations. When research is approved at CR with stipulations, the PI generally has thirty days to respond the stipulations. The thirty days is counted from the date the PI is notified of the stipulations. An IRB has discretion to give a PI more than thirty days to respond to stipulations, consistent with this policy.

Research is not considered to have lapsed if the research is approved with stipulations before the expiration date and final IRB approval is obtained no more than thirty days after the expiration. The research is considered lapsed if stipulations are not approved by the IRB within 30 days after the expiration date. If an IRB approval with stipulations

crosses over the expiration date, PIs should respond quickly to these stipulations to avoid a lapsed protocol.

If an IRB approves a CR with stipulations that go beyond the expiration date, the IRB must promptly inform OPS of the IRB decision and either instruct OPS to extend the expiration date on a reposted consent document, or provide a new consent to be posted.

9.12.4 Reporting Lapses to OHRP

A lapse in IRB approval is not required to be reported to OHRP as a protocol suspension or termination so long as no human subjects research occurs during this time period (aside from possible research performed in accordance with this policy in order to further a subject's best interest).

9.12.5 Lapses as Noncompliance

If the IRB notes a pattern of non-compliance with the requirements for continuing review, the IRB should determine whether this represents serious or continuing non-compliance that needs to be reported within NIH as described in SOP 16A.

9.13 Actions When IRB Approval Lapses and Research Expires

When the IRB Office has not received the CR Application or if the protocol has not been re-approved (with or without stipulations/conditions) by its expiration date, the IRB will notify the PI that all human subjects research under that protocol must stop and notify the OPS, IC CD and OHSRP that IRB approval has expired.

9.13.1 Actions at the Clinical Center

In the event that the IRB has not approved the Continuing Review (with or without stipulations) by midnight on the expiration date, the OPS will deactivate the research study from the NIH Clinical Research Information System (CRIS) and remove the consent/assent document(s) from the CC website for studies conducted at the NIH Clinical Center.

10.2 Policy

PIs are responsible for obtaining IRB approval of proposed amendments to an IRB-approved protocol before implementing them. The only exception to this requirement is when a change is necessary to eliminate apparent immediate hazards to subjects (see 45 CFR 46, **References** in SOP 10 and SOP 19).

10.4 Procedures for IRB Review and Clinical Director (CD) Review of Protocol Amendments

A. **Administrative Pre-review of Protocol Amendments:** The IRB administrative staff may pre-review amendment requests to assist the IRB chair to determine if the investigator submitted all necessary information. Pre-review may also be used to determine whether the amendment would be a minor change to the research and may be eligible for expedited review (see SOP 7A).

B. **Expedited Review of Amendments:** If the Chair or designee decides that the amendment is eligible for expedited review, it is reviewed according to SOP 7A.

C. Review of Amendments by the Convened IRB:

1. All IRB members receive all the submitted amendment materials and will have access to the complete IRB protocol.

2. IRB members must review the provided materials in order discuss them and vote at the meeting.

3. The IRB Chair may assign an IRB member to perform a primary review of the amendment and lead the discussion at the IRB meeting.

4. In reviewing the proposed amendment, the IRB should consider how it will affect the conduct of the study; whether it meets the regulatory criteria for approval (45 CFR 46.111); and whether or not it can be approved as written based on the IRB's risk/benefit assessment.

5. **The IRB can take the following actions on amendments:** unconditional approval, approval with stipulations, deferred approval, tabled or disapproved, as described in SOP 7.

6. The IRB will document in the minutes its discussion about and vote on the amendment and its determination whether current or past subjects must be

informed of the amendment, and, if so, how they will be informed (verbally and/or in writing). Current and past subjects must be notified if the study amendment affects their safety and welfare and current subjects re-consented if the amendment changes future clinical study procedures. Correspondence or other communications with subjects shall be submitted to and approved by the IRB.

7. The IRB votes separately on new amendments that accompany continuing reviews.

8. Clinical Director signatures/approvals are not required on all amendments. Each CD has authority to decide which IRB actions require CD approval, and they should communicate that information to the IRBs and to the CC Office of Protocol Services (OPS).

10.5 Notification of the IRB's Decision to Investigators

A. Investigators are notified in writing of the decision of the IRB and of any stipulations required. Amendments are not approved by the IRB until all stipulations have been satisfied.

B. The written amendment approval notification must state that further changes in research activity may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to subjects.

C. The PI may implement the changes provided in the amendment after IRB approval. If changes are required in the consent document, they are implemented after IRB approval and posting of the consent document by the OPS.

D. The continuing review date is not affected by the approval of amendments.

SOP 16 – Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations
Version 4, 3-14-2016

16.2 Policy

PIs must track and/or report UPs, PDs, AEs, and deaths. PIs report these events to their NIH IRBs, NIH Institute CD, and/or, if applicable, to the Sponsors of FDA-regulated research. The type and severity of the event dictates how quickly it must be reported and to whom.

The PI and IRB must determine whether the reportable event requires changes in the protocol or consent and whether other actions are needed to protect the safety, welfare, or rights of study participants or others. This SOP also describes requirements and time frames for NIH IRBs to review and report these events to the NIH Office of Human Subjects Research Protections (OHSRP), see **16.10.3** below.

PIs and Sponsor-investigators who are conducting protocols involving FDA-regulated research have additional Sponsor reporting requirements, some of which are described in Section 16.7 below. Other PI responsibilities related to FDA requirements are set forth in SOP 15; SOP 15A; and SOP 15B.

16.10 IRB Responsibilities

16.10.1. IRB Waiver of Certain IRB Reporting Requirements for Expected Events

In response to a PI's sufficient justification in the protocol, an IRB may agree to waive immediate and aggregate reporting requirements for a predetermined rate of anticipated PDs, expected non-UP AEs, or deaths based on the natural history of the disorder or population, (see **16.8.2** for additional details).

16.10.2 Initial IRB Receipt, Review, Determinations, and Actions regarding Reports of UPs and PDs

The review of UPs is the same for all studies; those involving no more than minimal risk are not treated differently from others. The IRB Chair/designee will review UP and PDs reports as soon as possible after receipt. He/she will determine whether the event should be submitted for review and a determination made and voted upon by the convened IRB at the next IRB meeting or at the protocol's next CR. Possible UPs and serious PDs must be discussed by the convened IRB at the next IRB meeting or sooner if necessary. The Chair/designee may act, as appropriate and consistent with law and NIH policy, to protect human subjects until the UP and/or PD is reviewed by the convened IRB.

If, in the IRB Chair/designee's judgment, immediate action is required to protect subjects--- such as suspension of the protocol, communication with enrolled subjects --- he/she shall inform the Institute CD, the Director CC (for protocols conducted at the NIH Clinical Center), and the NIH Office of Human Subjects Research Protections (OHSRP). The PI will also be informed in a timely manner.

16.10.3 IRB Review and Determination regarding Problem Reports

A. Problem Reports will be distributed for review by the entire IRB. At the discretion of the chair, either a primary reviewer or the entire IRB may review not serious PDs. Convened NIH IRBs will review PI problem reports forwarded by the IRB

Chair/designee and make an independent determination, documented in the minutes, about whether the event is a UP, non-compliance and/or a PD. The minutes should include whether the event affects the IRB's assessment of the risks and benefits of the protocol under 45 CFR 46.111. The IRB may determine it needs more information from the investigator, the Sponsor, the study coordinating center, or DSMB about the event(s).

B. In addition to its determination about whether an event is a UP or PD, and/or non-compliance, IRB actions may include, but are not limited to, the following:

1. No change is necessary to the protocol and/or consent document(s).
2. **Revision of the protocol and/or consent document(s):** The IRB will stipulate the required changes, which will be submitted by the PI as an amendment for future IRB review. The IRB will decide whether current subjects should be re-consented or informed by other means depending on the nature of the study.
3. **Suspension of enrollment:** Enrollment of new subjects on the study may be suspended by the IRB. The IRB will determine if, depending on the nature of the study, any current subjects may continue on the study or if subjects will be followed for safety purposes only, (see SOP 11).
4. **Termination of the study:** Subjects currently enrolled may be informed of the event and a plan will be submitted by the PI to the IRB for the safe withdrawal of remaining subjects.
5. Increased frequency/type of safety or other monitoring.
6. More frequent CR.
7. Recommendation for further evaluation and/or determination of possible Non-compliance, (see SOP 16A).

16.10.4 IRB Reporting of UPs to the NIH Office of Human Subjects Research Protections (OHSRP)

A. The IRB's UP reporting to OHSRP shall include:

1. The NIH Problem Report Form submitted by the PI to the IRB,
2. The IRB's determinations and/or actions, which may be addressed in the IRB section of the NIH Problem Report Form,
3. The IRB minutes (once available) containing its determinations and actions, and
4. Any other relevant documents, such as the IRB Chair/designee's initial evaluation, determination, and action (if applicable).

B. Once the IRB Chair or designee has determined that the PI's UP report should go to the convened IRB, that decision and a copy of the PI-submitted NIH Problem Report Form will be forwarded to OHSRP. Once the convened IRB has reviewed the UP, NIH IRBs are required to send any relevant documents, including the Problem Report Form with the IRB's determinations and actions, to OHSRP promptly. The IRB will also provide the minutes containing its determinations and actions to OHSRP within 7 days of approval of the minutes.

SOP 11 – Suspension and Terminations of IRB Approval and Administrative Holds
Version 3, 9-4-2015

11.2 Policy

An IRB may suspend or terminate a study if research is not being conducted in accordance with Federal regulatory requirements, IRB requirements, NIH policies, or if the study has been associated with unanticipated problems or serious harm to subjects. (See 45 CFR 46.113 and 21 CFR 56.113, if applicable.) Certain other NIH individuals and entities have authority to place an administrative hold on a protocol or close a protocol (see SOP 11A).

11.4 Entities Authorized to Request Suspension or Termination of IRB Approval

A. **Suspension:** The following parties may request suspension of an IRB approved research study:

1. The IRB Chair or Vice Chair, if delegated by the Chair.

2. Any IRB member or members at the convened IRB meeting.

3. The Institutional Official (IO) currently the Deputy Director of Intramural Research (DDIR) or designee.

4. Other senior NIH officials, such as the Institute Director/Clinical Director or Director, Clinical Center.

The IRB has the final authority for making determinations for actions characterized as suspensions, including whether and/or how an approved research study will be suspended.

B. **Termination:** The following parties may request termination of an IRB approved research study:

1. The IRB Chair or Vice Chair, if delegated by the Chair.

2. Any IRB member or members at the convened IRB meeting.

3. The Institutional Official (IO, the Deputy Director of Intramural Research (DDIR)) or designee.

4. Other senior NIH officials, such as the Institute Director/Clinical Director or Director, Clinical Center.

The IRB has the final authority for making determinations for actions characterized as terminations, including whether and/or how an approved research study will be terminated.

C. Data from terminated protocols may be used for research purposes only after the proposed new research receives prospective approval by an NIH IRB or, when appropriate, OHSRP/IC designee (see SOP 5).

11.5 Required IRB Actions Related to Suspension or Termination

A. **Urgent situations:** The IRB Chair/designee may suspend a protocol in an urgent situation if, in his/her judgment, immediate action is required to protect subjects. See Revised SOP 16). However, the full IRB must convene and vote regarding action to terminate a protocol.

B. Upon the IRB's determination to suspend or terminate all or some parts of a research study, the IRB will promptly notify the PI in writing of:

1. The IRB's decision, including a statement of the reasons for the suspension/termination. The investigator will be given an opportunity to respond in writing.

2. Work with the PI to develop a plan to protect the rights, safety and welfare of enrolled subjects, if any.

3. Review, and take action on as needed, the PI's termination/suspension plan (including as described in **11.6.A.4**, below). The IRB will notify the PI and the CC, Office of Protocol Services (OPS), in writing, of what activities, if any, are authorized to continue and conditions for such continuation.

C. The IRB may require that subjects be informed of the suspension/termination. Written communication to the subjects requires prospective IRB approval.

D. Prospective IRB approval must be obtained if the researchers wish to re-contact former subjects after study termination to provide the subjects with additional study-related information.

11.6 IRB Notification of Suspension or Termination

A. Upon suspension or termination by the IRB, the IRB will notify the PI, IC leadership (Clinical Director), OPS and OHSRP. The Director of the Clinical Center will be notified by the IRB of any suspensions or terminations occurring on protocols implemented in the Clinical Center. The IRB will stipulate that for terminations, the PI will submit a Clinical Study Closure Application consistent with SOP 11 A and, as applicable, provide responses to items noted in **section 11.7**. The IRB notification will include the following information:

1. The reasons for the suspension or termination.

2. The effective date of the suspension or termination.

3. Delineation of the effect of the suspension or termination on study activities such as enrollment, recruitment, interventions, interactions and data analysis.

4. PI responsibilities (**section 11.7** below) with regard to the suspension or termination.

11.8 Resumption of Research Activities after a Suspension

B. An NIH IRB can approve resumption of suspended research activities if the issues that led to the suspension have been resolved. If a PI wishes to request removal of the suspension, the PI must submit a written memorandum with the following information:

1. Justification for resumption.

2. Identification of the issues leading to the suspension and explanation of how they have been resolved.

3. A description of any changes needed to the protocol or consent document(s) in response to the issues related to the suspension.

A formal amendment (request for modification) must be separately submitted for IRB approval before any changes can be implemented (see SOP 10).

11.10 Reporting Suspensions and Terminations to NIH Institutional Officials and Regulatory Agencies

A. The NIH IRB will notify, as soon as possible, the Institutional Official (the DDIR) through the OHSRP, as well as IC leadership (the Clinical Director) and OPS of any suspensions or terminations of studies. The Director of the Clinical Center will be notified by the IRB of any suspensions or terminations occurring on protocols implemented in the Clinical Center (CC). The IRB, or its designee, will ensure that officials at non-CC study locations are informed about suspensions and terminations, as appropriate, after such a determination is made by an NIH IRB.

B. The OHSRP and the IRB will comply with the reporting requirements of the appropriate regulatory agency and take appropriate actions per SOP 24.

11.11 Administrative Hold

An investigator may institute an administrative hold on a study when he/she wishes temporarily to stop, or as a preliminary step before permanently stopping, some or all approved research activities. An administrative hold may be in response to a directive from a sponsor, or FDA or other authorized review body. Senior NIH officials, such as the Institute Director/Clinical Director or Director, Clinical Center, may request an administrative hold for NIH institutional reasons, e.g., loss of funding, departure of the PI from NIH.

Administrative holds are not suspensions or terminations, and are not an IRB directive requiring notification to OHRP, but the IRB needs to be notified of administrative holds to ensure that the rights and welfare of subjects are protected. Studies on administrative hold require continuing review by the IRB prior to the expiration date. The procedures for initiating and implementing an administrative hold are:

A. The Principal Investigator must notify the IRB in writing within five days of the action that he/she is voluntarily initiating an administrative hold on the study.

B. The administrative hold notification is submitted as an amendment and must include a description of the research activities that will be put on hold.

C. A justification for the administrative hold and any supporting documentation that include the proposed actions to protect and notify currently enrolled subjects.

Upon receipt of written hold notification, an administrative hold notice is treated as an amendment to the previously approved research using the protocol review standards for amendments. (see SOP 7). The amendment may receive expedited review, if applicable. The IRB staff includes the request on the IRB meeting agenda for review.

D. The IRB Chair or the convened IRB reviews the hold actions and determines whether any additional procedures need to be followed to protect the rights, safety and welfare of currently enrolled subjects.

E. The IRB Chair or the convened IRB notifies the PI of any additional procedures that need to be followed to protect the rights, safety and welfare of currently enrolled subjects.

F. The IRB will notify the IC and, where applicable, the CC, Office of Protocol Services (OPS), in writing, of what activities, if any, are authorized to continue and conditions for such continuation. The IRB should indicate if the current consent form should remain posted or not.

G. When the entire protocol is placed on administrative hold, the accrual status changes to “Clinical Hold/Recruitment or enrollment suspended” in OPS. On clinicaltrials.gov the status will appear as suspended, which indicates that participant recruitment and enrollment has halted but potentially will resume.

SOP 16A – Allegations of Non-Compliance with Requirements of the NIH Human Research Protection Program (HRPP)
Version 3, 3-17-2016

16A.2 Policy

NIH strongly encourages persons to report, through proper channels, all observed or apparent incidents of non-compliance. These incidents may concern active or closed protocols or non-protocol issues related to HRPP policies.

It is the policy of the NIH Human Research Protection Program (HRPP) to investigate allegations of non-compliance with NIH HRPP policy and other requirements in a methodical and fair manner and, if necessary, to take corrective action commensurate with the nature and degree of non-compliance. The type of allegation determines the process, as set forth in this Standard Operating Procedure (SOP). When the allegation regards an active protocol, NIH Institutional Review Boards (IRBs) are the primary entities responsible for conducting the investigation of non-compliance. When an allegation regards non-compliance by an NIH IRB, or NIH official, or involves other aspects of the HRPP not related to an active protocol, the Deputy Director for Intramural Research (DDIR) determines who will conduct the investigation of non-compliance. The Office of Human Subjects Research Protections (OHSRP) may also participate in these activities, depending on the nature of the issue.

This SOP does not explain the separate process by which Principal investigators (PIs) are required to self-report certain instances of non-compliance related to protocols and the IRB review of such reports. (For more information, see **16A.7.2** and the process detailed in SOP 16.)

16A.5 Response to Possible Serious and/or Continuing Non-Compliance

At any point in this process, if any individual or entity considers that serious and/or continuing non-compliance has occurred or is likely to occur, the individual or entity should notify the IRB and, if authorized, s/he may decide that research should be placed on an administrative hold. The IRB has the authority to suspend the protocol (see SOP 11).

16A.7.3 IRB Actions

After an IRB determination of non-compliance is made, possible actions include:

A. **Action on a finding of minor non-compliance:** The IRB may allow the research to continue with no further action required or may require modifications that

constitute a minor change in the research. If changes to the research protocol are required, the PI will submit an amendment to the IRB. Minor changes to previously approved research may be eligible for review under expedited review procedures consistent with the requirements of SOP 7A.

B. **Action on a finding of serious and/or continuing non-compliance:** The IRB will take prompt and appropriate action to assure the safety and welfare of human research subjects and the integrity of the research. These actions may include, but are not limited to, the following:

1. Require modifications in the protocol and/or consent document(s), or require consent monitoring.

2. Require that subjects who are still participating in the research be notified of the non-compliance and/or re-consented.

3. Require, if appropriate, that subjects whose participation has ended be notified of the non-compliance.

4. Modify the continuing review schedule.

5. Suspend the research (see SOP 11).

6. Terminate the research (see SOP 11).

7. Require monitoring of the research by a QI/QA team (see SOP 23) and/or the IRB.

8. Require educational measures for researchers/research staff.

9. Any other remedial or corrective action the IRB deems appropriate.

C. **Non-HRPP issues:** The investigation of possible non-compliance may uncover issues that are not under the HRPP purview of OHSRP or the IRB. For example, poor record keeping or inadequate supervision of clinical procedures not related to the human subjects research might not be a matter of HRPP compliance. The IRB/OHSRP may not make determinations about these issues, but may refer their concerns to other appropriate entities such as the IC or Clinical Center, to address appropriately, consistent with applicable law and NIH Policies.

16A.10 IRB and OHSRP Reporting to NIH Officials and Other Entities

A. At any point during the proceeding, if a convened IRB or OHSRP determines that facts suggest serious and/or continuing non-compliance, the appropriate NIH officials will be notified (e.g., the DDIR, the appropriate Clinical Director, and/or other IC officials).

B. Determinations of serious and/or continuing non-compliance will be reported to OHSRP.

C. Reporting to OHRP and the FDA will be handled according to SOP 24. The IRB has no responsibility to initiate any public disclosure of the findings.

D. If there is evidence of a possible violation of the NIH policy on misconduct in scientific research, the matter will be forwarded to the NIH Agency Intramural Research Integrity Officer (AIRIO) for further action.

SOP 17 – Data and Safety Monitoring
Version 2, 3-8-2016

17.2 Policy

In accordance with regulatory requirements (45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6) Criteria for IRB approval of research and 21 CFR 50.24(a)(7)(iv) Exception from informed consent requirements for emergency research), the NIH Human Research Protection Program (HRPP) requires inclusion of data and safety monitoring plans (DSMPs) in all research protocols submitted to NIH IRBs. The IC, the FDA or an IRB can require that a DSMP identify an independent data and safety monitoring entity (e.g. a medical monitor or a Data and Safety and Monitoring Board). When DSMPs involve monitoring of research by an NIH Data and Safety and Monitoring Board (DSMB), Institute officials are responsible for DSMB organization, consistent with their Institutes' written procedures.

17.5 Responsibilities of PIs, IRBs, Monitoring Entities, and Institute Officials

A. IRB Responsibilities:

1. **Reviewing and approving the DSMP:** The IRB reviews the DSMP in the protocol to determine whether it makes adequate provisions to ensure, to the extent possible, the safety of research subjects and the integrity of the data. As applicable, the IRB will include in its review, the criteria set forth in **17.4.B.-G**. An IRB-approved DSMP is required before research begins.

2. **Reviewing data and safety monitoring entity's reports**: The IRB Chair reviews data and safety monitoring reports as they are received. The Chair has the discretion to recommend review by the convened IRB at any time. The IRB should review all monitoring reports since the date of the last IRB review and approval of the project at the time of continuing review:

a. Information regarding any unanticipated problems that have occurred since the previous IRB review will be pertinent to the IRB's determinations regarding the risk/benefit ratio of the study.

b. It also may be appropriate for the IRB to confirm that any provisions for monitoring the data to ensure safety of research subjects, contained in the previously approved protocol, have been implemented and are working as intended (45 CFR 46.111(a)(6)).

3. **Reviewing the PI's proposed actions, based on monitoring report findings:** The IRB will review actions proposed by the PI, e.g. protocol amendments, an administrative hold or closure, that are based on the data and safety monitoring entity's recommendations.

SOP 11A – Closure of an IRB-Approved Protocol
Version 2, 8-17-2015

11A.2 Policy

Principal Investigators (PIs) are responsible for notifying the IRB whenever an IRB-approved study will be closed, regardless of the reason for closure. Data collection and analysis for the study are not permissible after study closure.[1]

11A.5 Procedures for IRB Review of Protocol Closure

The NIH IRB has the following responsibilities at the time of study closure:

A. Review the Intramural Clinical Protocol Study Closure Application submitted by the PI.

B. Study Closure may undergo expedited review if the criteria for expedited review are met (see SOP 7A).

C. Confirm that the PI has developed an appropriate plan for the disposition of specimens (see SOP 5 and SOP 6) and approve the plan, for example:

   1. Specimens will be used up or destroyed.

   2. Specimens will retain identifiers or be coded and be transferred for another IRB-approved protocol and/or stored for future use.

[1] Study data and/or samples may be used if transferred to another IRB approved protocol or an OHSRP/IC designee exemption has been obtained. See **section 11.A.5.C and 11.A.5.D.**

3. Specimens will be irreversibly stripped of all identifiers and stored for future use in a NIH-controlled freezer.

4. Specimens will be transferred to a repository for future use.

D. Confirm that the PI has developed an appropriate plan for the disposition of data and approve the plan, for example:

1. Data with codes/identifiers will be transferred for use by another IRB-approved protocol and/or stored for future use.

2. Data will be irreversibly stripped of all identifiers and stored for future use.

E. Data and specimens must be stored according to applicable law, policy and regulations.

F. If premature closure of a study is anticipated (e.g., the study is to be closed earlier than anticipated based on recommendation of the DSMB), the IRB should work with the PI to develop a plan to ensure that the rights and welfare of currently enrolled subjects are protected. (see **Section 11A.4.D** above)

G. In accord with Revised SOP 4, IRB records relating to the protocol shall be retained for at least 3 years after completion of the research.

CHAPTER 3: INTERACTIONS WITH SUBJECTS AND VULNERABLE POPULATIONS

SOP 12 – Requirements for Informed Consent

Version 4, 3-7-2016

12.2 Policy

Except as provided elsewhere in this SOP (see **Sections 12.10, 12.11, 12.12** and **12.13** below), no investigator may involve a human as a subject in research covered by this policy unless the investigator has obtained the subject's legally effective informed consent. Before any research procedures are initiated, NIH requires written informed consent from research subjects, or their legally authorized representatives (LAR) for an adult (see 14E - Research Involving Adults Who Are or May be Unable to Consent), or the permission of parent(s) or guardian(s) for a minor (see 14D - Research Involving Children). Written informed consent is required unless informed consent and/or the written consent document is waived by an Institutional Review Board (IRB), consistent with requirements in this SOP (see **12.10**, **12.11, 12.12** and **12.13** below). For more

information about FDA requirements, see SOP 15. For specific requirements about obtaining consent or assent from vulnerable populations, see SOPs 14B, 14C, 14D, 14E and 14F.

12.7 Approval of Informed Consent

A. Written consent documents shall be approved by the IRB at the same time as the written research protocols. Amendments or other changes in the approved protocol that may affect informed consent shall be incorporated into a revised consent document and approved by the IRB prior to use. Minor changes may sometimes be approved by expedited review. The consent document shall be reviewed and approved by the IRB at least once a year.

B. Consent documents and protocols involving the research use of ionizing radiation shall also be reviewed by the Radiation Safety Committee and, if indicated, by the Radioactive Drug Research Committee. Protocols may also require additional review, depending on the type of research, by other committees such as the Recombinant DNA Advisory Committee or the Institutional Biosafety Committee.

C. In certain circumstances prescribed by the Federal regulations (45 CFR 46 and, as applicable, 21 CFR 50), an IRB may waive the requirement to obtain informed consent, or may approve a consent process which alters or does not include some of the required elements (see **Sections 12.10, 12.11, 12.12** and **12.13**, below.)

D. The IRB has the authority to have IRB members observe or monitor the consent process or to require an impartial third party observe or monitor the consent process (see **Section 12.16** below).

E. The informed consent process is an ongoing discussion about the study, and continues after the informed consent form is signed. For instance, when new risk information relevant to a subject's ongoing participation is discovered, notification to the subject may be required by the IRB (for more information, see SOP 16).

F. Except when the IRB waives the requirement (45 CFR 46.117(c), see **Section 12.11** below), the informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject (45 CFR 46.117).

G. Sample or draft consent documents may be developed by a sponsor or cooperative study group for review by IRBs in participating organizations. However, NIH IRBs

have the final authority for the content of consent documents to be used in protocols in which NIH IRBs are responsible for reviewing the research.

12.7.2 Types of Written Research Consent Documents

A. An NIH IRB may approve the following written consent documents (45 CFR 46.117(b) and 21 CFR 50.27(b)):

1. A written consent document (long form) that embodies the elements of informed consent found in 45 CFR 46.116 (see **12.4.1**). The consent form may be read to the subject, but the subject must be given adequate opportunity to read it before it is signed; or

2. A short form written consent document stating that the required elements of informed consent from 45 CFR 46.116 have been presented orally to the subject. (Use of a short form may be appropriate for unexpected enrollment of non-English speaking (see **12.9.1.B**) or blind (see **12.9.2**) subjects as approved by the IRB).

B. When the short form document is used:

1. The IRB must approve the short form document and a written summary of what is to be said to the subject.

   a. For subjects at the NIH CC, if there is no IRB-approved short form consent for use on the CC Active Consent/Assent webpage, the IRB must approve the short form that will be used to document the subject's signature (unless waived by the IRB) with the oral presentation, for more information see Sections **12.8.3** and **12.9.1** below.

2. There must be a witness to the oral presentation.

12.8.2 Provision of Preliminary Information to Prospective Subjects

In order to provide preliminary study information to prospective subjects, investigators, or others on the research team, may discuss the proposed research with them before consent is obtained and formally documented so long as such communication is prospectively approved by the IRB. Such communications may include face-to-face conversations, postal mail, e-mail, telephone, facsimile, or other methods of communication. NIH allows interaction with prospective subjects without IRB approval if the interaction is not considered engagement in human subjects research per Office for Human Research Protections (OHRP) guidance. See the link to the OHRP "Guidance

on Engagement of Institutions in Human Subjects Research" (section B, Part 4) in **References** in SOP 12.

12.8.4 Informed Consent Documentation

A. Informed consent shall be documented using the current IRB-approved consent form, except where this written requirement is waived by the IRB.

1. At the CC, IRB-approved consents/assents must be downloaded from the CC active consent website (see **References** in SOP 12).

B. Required signatures on informed consent documents are specified below:

1. **English or translated long form consent:** When consent is obtained, the consent document(s) must be signed and dated by the subject, and the person obtaining consent.

12.9.1 Non-English Speaking Subjects

No one should be excluded from the consent process on the basis of language alone. For non-English speaking subjects, the consent process should occur as provided in **12.9.1 A, B** and **C** below.

The consent document (long or short form) should be written in a language that the subject can understand (e.g., in Spanish for a Spanish-speaking subject), as provided at **12.9.A.1** and **12.9.1.B.2** below, and, as necessary, a translator must be used during the consent process. To assure the consent form translation is accurate; the IRB may require a certified translation of the consent language without additional back-translation. If no certified translation is available, a non-certified translation may be used, and an independent back-translation must also be obtained.

A. Expected enrollment of non-English speaking subjects:

1. In studies where the PI expects non-English speaking subjects to be screened or enrolled, translation and IRB approval of the long form consent document is required.

B. Unexpected enrollment of non-English speaking subjects:

1. If a non-English speaking subject is unexpectedly enrolled in a study, there may not be an existing IRB-approved written translation of the consent document.

2. The IRB must approve the use of the short form process and the translated short form. The IRB must receive all foreign language versions of the short form document as a condition of approval under the provisions of 45 CFR 46.117(b)(2). See **item 4** below for more information about the use of IRB-approved translations of short-form consents on the CC Consent/Assent website. The IRB must approve the written summary statement provided to the subject, which may be the long form consent document.

3. When a short form and oral presentation are used with subjects who do not speak English, (i) the oral presentation and the short form written document should be in a language understandable to the subject; and (ii) the IRB-approved English language informed consent document may serve as the summary.

4. For subjects at the CC:

   a. If a short-form consent in the subject's language is available and posted on the CC website (see **References** in SOP 12) follow the procedures for a short form written consent as described in **12.8.4.B.3** and **12.8.4.C.2** above, once the IRB has approved the use of the short form process and the summary statement (**12.9.B.2**). All NIH IRBs have approved these translated short forms.

   b. For non-English speaking subjects for whom no written language exists, the English short form consent may be used with an interpreter and the IRB-approved English consent as the basis of oral translation, unless the IRB waives this requirement and provides an alternate plan for informed consent.

5. Expedited review of the short form consent process may be used if the protocol and the long form informed consent document have already been approved by the IRB.

6. The witness to a short form consent process is frequently, but not always, conversant in the language of the participant. (The NIH subject population is extremely diverse and researchers cannot always obtain a witness fluent in the participant's language.)

C. **Use of interpreters in the consent process:** Unless the person obtaining consent is fluent in the prospective subject's language, an interpreter will be necessary to deliver information in the IRB-approved oral consent process. It is preferable that

someone who is independent of the subject (e.g., not a close family member, significant other, partner, etc.) be the interpreter.

12.9.2 Blind, Illiterate or Disabled Subjects

An investigator must document the method used for communication with the prospective subject in the subject's research record (and, if at the CC, in the subject's medical record) and must document the specific means by which the prospective subject communicated agreement to participate in the study.

A. For blind subjects, the IRB may approve a consent document prepared in Braille for blind subjects who read Braille. In order to assure itself that a Braille consent document is accurate; the IRB may require a transcription into print text or a certified review of the document by an IRB member or other person who reads Braille. The printed text should be filed in the record with the Braille consent. If possible, the subject will sign the Braille consent; otherwise oral short form consent will be obtained consistent with **12.8.4.B.2** and **12.8.4.C.2** above.

B. In the case of where disability prevents subjects from being able to physically sign his/her name, or in the case of illiterate subjects, the subjects can be enrolled in a study by "making their mark" on the consent document (long or short-form as applicable), and as applicable, when consistent with state law.

C. The PI must seek, and the IRB may approve, the use of assistive technology (e.g., audiotape) to aid subjects (e.g., those that are illiterate or blind) to review the consent form content.

D. A subject who is physically unable to make their mark and unable to speak can be entered into a study if they are competent and able to indicate approval or disapproval by other means approved by the IRB.

E. IRBs may consider approving the short form consent process in situations where the subject is unable to read the consent form due to illiteracy or blindness.

F. Waiver of documentation of informed consent must have IRB approval consistent with 45 CFR 46.117 and **Section 12.11** below.

12.10 Waiving or Altering Elements of Informed Consent under 45 CFR 46

A. **Circumstances in which the IRB may waive or alter elements of the informed consent procedure or waive the requirements to obtain informed consent:** An NIH IRB may approve a consent procedure that does not include, or which alters some, or all, of the elements of informed consent set forth in 45 CFR 46.116(a-b), or waive the requirements to obtain informed consent, provided the IRB finds and documents in the IRB meeting minutes:

1. The research involves no more than minimal risk to the subjects.

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.

3. The research could not practicably be carried out without the waiver or alteration, and

4. Whenever appropriate, the subjects must be provided with additional pertinent information after participation (see 45 CFR 46.116(d), link also in **References** in SOP 12).

B. An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent or waive the requirement to obtain informed consent provided the IRB finds and documents that:

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

2. The research could not practicably be carried out without the waiver or alteration (see 45 CFR 46.116(c)).

12.11 Waiver of The Requirement to Document Informed Consent In Writing under 45 CFR 46

A. The IRB may waive the requirement for the investigator to obtain a signed consent form from some or all subjects provided the IRB finds and documents that either:

1. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach

of confidentiality. Each subject will be asked whether he/she wants documentation linking the subject with the research, and the subject's wishes will govern (45 CFR 46.117(c)(1)) (for example: domestic violence research where the primary risk is discovery by the abuser that the subject is talking to researchers); or

2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context (45 CFR 46.117(c)(2)). (Examples include drawing a blood sample, or asking shoppers in a mall about the ambient lighting or temperature).

B. When the IRB considers waiving the requirement to obtain written documentation of the consent process, the IRB reviews a written description of the information that will be provided either verbally or in writing to participants. This may be a script or a statement about what information will be conveyed.

C. **Waiver of Parental or Guardian Consent:** In addition to the provisions for waiver contained in §46.116 of subpart A, if the IRB determines and documents that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A and 45 CFR 46.408(b), provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with applicable federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition (45 CFR 46.408(c).

12.12 Waiver of the Requirement to Document Informed Consent inn Writing under 21 CFR 56 (as applicable)

FDA-regulated research, when applicable: The IRB may waive documentation of informed consent as described in SOP 15A (21 CFR 56.109(c)). The IRB must document the waiver in the IRB Minutes. When the IRB considers waiving the requirement to obtain written documentation of the consent process, the IRB reviews a written description of the information that will be provided either verbally or in writing to participants. This may be a script or a statement about what information will be conveyed.

12.15 Obtaining Consent by Telephone

For research protocols or any procedures performed for research purposes in which the investigator intends to obtain consent from a subject who is not in the same location as the investigator, for example, for specimen collection or interview, consent may be obtained via telephone and/or another electronic process, rather than in person. The procedures for obtaining consent, including how the consent document and/or other information will be transmitted and documented and by whom, shall be described in the written protocol. Prospective IRB review and approval is required. If eligible, the IRB may choose to review such requests through the expedited review procedure. A written signed consent must be faxed and/or mailed and made part of the record unless the IRB waives written consent (see **12.10** and **12.11**, above, waiving or altering elements of informed consent.

Except in the examples above, or in extraordinary circumstances, research consent should normally be obtained in person.

12.16 Consent Monitoring

12.16.1 Consent Monitoring by an IRB or Authorized Third Party

DHHS Federal regulations allow an IRB, or an authorized third party, to observe the consent process and the research (45 CFR 46.109(e)).

A. An NIH IRB may determine that monitoring of the consent process by an impartial observer (consent monitor) is required. For example, such monitoring may be warranted for:

1. High risk studies.

2. Studies that involve particularly complicated procedures or interventions.

3. Studies involving vulnerable populations.

4. Other situations when the IRB has concerns that the consent process may not be conducted appropriately, for example, to reduce the possibility of coercion and undue influence, to ensure that the approved consent process is being followed, or to ensure that subjects are capable of giving informed consent.

5. As a corrective action where the IRB has identified problems associated with a particular investigator or a research project (see SOP 16A).

B. Development of a consent monitoring plan:

1. If the IRB determines that consent monitoring is required, the PI will develop a consent monitoring plan for review and approval by the IRB. The consent monitoring may be conducted by qualified persons including IRB members or others, either affiliated or unaffiliated with the NIH.

2. At the NIH CC, the Department of Bioethics consult service is available for consent monitoring (i.e. CC Department of Bioethics Ability to Consent Assessment Team (ACAT).

3. NIMH Human Subject Protection Unit (HSPU) also provides consent monitoring as well as other monitoring or consultative services and consent training for investigators and research staff. For more information, see **References** in SOP 12.

4. When the IRB determines that consent monitoring is appropriate, the PI will be notified in writing including the reasons for the determination. The determination will also be noted in the IRB minutes/record.

SOP 13 – Recruitment, Selection and Compensation of Research Subjects
Version 3, 9-4-2015

13.2 Policy

During the initial review (IR) of protocols, NIH IRBs will review and approve recruitment and compensation plans proposed by PIs. At the time of continuing review (CR), IRBs will evaluate whether the protocol has accrued subjects in accord with the IRB-approved selection criteria.

13.3.3 IRB Responsibilities [General Considerations]

A. **IR:** The IRB reviews and approves the protocol consistent with SOP 8, including the rationale for research subject selection, the strategies and procedures for recruiting subjects (see **13.4** below) and any justification(s) for exclusion of women and/or individuals from particular population categories.

1. **In determining if subject selection is equitable, the IRB will consider a variety of factors, including but not limited to:** the purposes of the research; the inclusion/exclusion criteria; the setting in which the research will take place; whether prospective subjects are vulnerable to coercion or undue influence, recruitment/enrollment procedures (see **13.4.2** below), and the amount and timing of compensation, if any (see **13.5** below).

2. Exclusion of certain populations, such as children, should be justified based on the nature of the disease or condition being studied, or for other scientific, ethical or safety reasons (e.g., see SOP 14D and the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" in **References** in SOP 13).

3. The IRB will forward the IC-approved Planned or Cumulative Enrollment Report, as applicable to the Office of Protocol Services (OPS) to be tabulated and reported.

B. **CR:** The IRB will review the Memorandum of Progress for the enrollment and retention of subjects to assess the consistency with the recruitment plan in the protocol, see **13.3.2.A** above and SOP 9.

1. If slow enrollment or loss of subjects on the study jeopardizes the scientific integrity of the research or no longer justifies the continued enrollment of subjects, and/or if the IRB finds that the cumulative enrollment is inconsistent with previously approved targets for subject selection (see Section **13.3.2.A**, above), the IRB has broad discretion in exercising its judgment on how to proceed. Its actions may include:

   a. Continuation of subject accrual, with or without a request that the PI provide a plan for improved accrual, or

   b. If necessary, referral of the matter to the IC Clinical Director for evaluation of recruitment strategies and additional resources, or

   c. Suspension or termination of the protocol for failure to meet the terms and conditions of IRB approval.

2. The IRB will forward the IC-approved Cumulative Enrollment Report to the Office of Protocol Services (OPS) to be tabulated and reported.

13.4.3 IRB Responsibilities [Regarding Recruitment Procedures and Materials]

The IRB will review and must approve recruitment materials before they are used. This includes the information contained in the materials, how the information is to be communicated, and the planned venue(s) for distribution (for example, newspaper, radio, or flyer). For audio/video tape, the IRB may review and approve the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording. The IRB will review the final copy of printed and/or electronic advertisements and the final version of audio- or videotaped advertisements and may use expedited procedures for final approval.

A. **Verification of information and institutional logos:** The IRB will verify that all information included in the recruitment materials is consistent with the protocol. DHHS, NIH, and IC logos must be used consistently with NIH Policy Manual 1186, "Use of NIH Names and Logos" (see **References** in SOP 13).

B. **Recruitment Materials:** As part of its review of recruitment materials, the IRB will ensure that materials do not:

1. State or imply a favorable outcome or other benefits beyond what is stated in the protocol and the consent document.

2. Include exculpatory language.

3. Emphasize monetary compensation or the amount to be paid by such means as larger or bolder type.

4. Promise "free treatment" when the intent is only to say participants will not be charged for taking part in the investigation.

5. IRBs should pay particular attention to risk and potential benefit information to ensure it is presented in a balanced and fair manner. If identifiable private information of prospective subjects is to be collected via a clinical trial website, the IRB should review plans for protecting the confidentiality of that information. The IRB should ensure that the website clearly explains how identifiable private information might be used. For further guidance, see OHRP "Guidance on IRB review of Clinical Trial Websites" (see **References** in SOP 13).

C. **Recruitment Materials related to FDA-regulated research:** As part of its review, the IRB will ensure that recruitment materials are consistent with FDA regulations and applicable guidance, (e.g., "Recruiting Study Subjects - Information Sheet: Guidance for IRBs and Clinical Investigators", see **References** in SOP 13).

13.5.3 IRB Responsibilities [Regarding Compensation of Research Subjects]

A. **General considerations:** The IRB shall review the justification for compensation to ensure it is appropriate given the particular study and the population to be recruited, and that the compensation payments are reasonable, equitable, and do not constitute coercion or undue influence. In making this decision, the IRB should consider the potential vulnerabilities of the targeted subject population and the proposed methods for assessing subjects' knowledge of risks and benefits and their ability to make voluntary, autonomous decisions. It should also take into account the amount, schedule, and method of disbursement of compensation payments.

B. **Review and approval of the proposed compensation plan:** The IRB reviews and determines that the amount of payment and the proposed method and timing of compensation is appropriate (does not present undue influence). In making that determination, the IRB shall verify that:

   1. As appropriate, credit for compensation payments accrue as the study progresses and are not contingent upon the participant completing the entire study, and

   2. Any amount paid for completion of the study is reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.

C. The IRB shall be satisfied that the NIH/CC (or local non-CC) guidelines for calculating amounts have been followed, or that justification provided for any deviation is appropriate. See **Appendix A - Guidance for Monetary Compensation for Clinical Research Volunteers** and **Appendix B - Worksheet/Tool for Calculating Estimated Compensation**, in SOP 13 for more information.

D. **Review and approval of the consent document language:** The IRB shall assure that all relevant information concerning compensation, including the amount and schedule of payments, is set forth in the consent document.

SOP 18 – Privacy and Confidentiality
Version 2, 3-2-2016

18.2 Policy

This policy establishes procedures for the NIH Human Research Protection Program (HRPP) to maximize research subjects' privacy and to maintain the confidentiality of their personally identifiable information. In its human research and record-keeping activities, the NIH HRPP follows the requirements of the Privacy Act, 5 U.S.C. 552a (see **References** and **Section 18.4.1** in SOP 18).

18.5 Privacy

18.5.1 General Considerations

IRBs should assure that privacy protections are in place. The IRB should consider the circumstances under which research staff interact with subjects and collect their personal information.

18.5.4 IRB Responsibilities [Regarding Privacy]

The IRB reviews the PI's plan related to protecting research subjects' privacy (see SOP 8).

As part of its review, the IRB will consider the specific research activities in the protocol, the protections outlined in **Section 18.5.2**, and the requirements of SOPs 7, 7A, 7B, and 8.

The IRB will determine whether adequate procedures are in place to protect the privacy of subjects, in the context of the specific research activities included in the protocol.

The IRB will review and approve language in informed consent document(s) related to privacy (see **Section 18.7**).

18.6.2 IRB Responsibilities [Regarding Confidentiality]

The IRB will review the protocol to assure that confidentiality protections provided by the PI (see **Section 18.6.1**) are consistent with NIH requirements and commensurate with the degree of risk of harm from improper disclosure.

18.6.3 Certificate of Confidentiality

A PI may request or the IRB may require a Certificate of Confidentiality (COC) for a research study (see **Section 18.3.A** and **References** in SOP 18). Certificates of Confidentiality are granted by the Federal government, upon request and in its discretion, for studies collecting information that, if disclosed, could have adverse consequences for research subjects or damage their financial standing, employability, insurability, or reputation. The COC does not protect against voluntary disclosure by an investigator or the NIH, for example, in cases of abuse or reportable communicable diseases or when a research subject gives written authorization for the release of

identifiable information. Types of research that may be eligible for a Certificate of Confidentiality include, but are not limited to:

Research on HIV, AIDS, and other sexually transmitted diseases (STDs);

Studies that collect information on sexual attitudes, preferences, or practices;

Studies on the use of alcohol, drugs, or other addictive products;

Studies that collect information on illegal conduct;

Studies that gather information that if released could be damaging to a subject's financial standing, employability, or reputation within the community;

Research involving information that might lead to social stigmatization or discrimination if it were disclosed;

Research on subjects' psychological wellbeing or mental health;

Genetic studies, including those that collect and store biological samples for future use; and

Research on behavioral interventions and epidemiologic studies.

The PI is responsible for obtaining and maintaining the COC during the research study and providing COC documentation to the IRB (see **Section 18.6.3.A**).

18.7 Privacy and Confidentiality Language in Informed Consent Documents

A. The IRB reviews and approves language in the informed consent documents related to privacy and confidentiality.

1. NIH has standard language, approved by the NIH Office of General Counsel (OGC), which is included in all NIH consent documents (NIH 2514-1):

   "Confidentiality: When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

   The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from

your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized accreditation organizations."

IRBs may require additional language in the body of the consent, as they deem appropriate, but any change in the NIH standard language requires prospective approval by NIH OGC.

B. The IRB will assure that adequate information about the Certificate of Confidentiality (COC), when applicable, appears in the consent document (see Section 18.6.3). Suggested consent language may be found at the Certificates of Confidentiality Kiosk (see **References** in SOP 18).

SOP 14A – Research Involving Vulnerable Subjects (General Considerations)
Version 2, 12-01-2015

14A.2 Policy

The NIH Human Research Protection Program (HRPP) abides by Federal regulatory requirements to provide appropriate additional protections for vulnerable subjects (Department of Health and Human Services (DHHS) regulations at 45 CFR 46.111(b) and, if applicable, FDA regulations at 21 CFR 56.111(b)).

14A.3.3 Additional NIH Requirements

A. In addition to the requirements of **14A.3.1** and **14A.3.2** above, the NIH HRPP has additional protections for adult subjects who are or may be unable to consent (see SOP 14E) and for subjects who are also NIH staff (see SOP 14F).

B. In addition to the specific protections required under 45 CFR 46 Subparts B, C and D, the NIH HRPP expects IRBs to use their judgment when determining if subjects enrolling into particular protocols are considered vulnerable and if additional protections are warranted. For example, students and very ill persons may be considered vulnerable subjects.

14A.4 Procedures for the Initial Review of a Research Study Involving Vulnerable Subjects

B. The policy of other relevant SOPs on initial review of research applies when vulnerable populations are the anticipated subjects. Relevant SOPs include: SOP 7, SOP 7A, and SOP 8. At NIH, expedited review for minimal risk studies including vulnerable subjects is permitted generally, but expedited review is not permitted for any research involving prisoners.

C. The PI will complete the NIH Intramural Clinical Initial Protocol Application and ensure that the protocol contains the information described in the Supplements relevant to the subjects to be enrolled, i.e., Supplement D (Children), Supplement E (Prisoners), Supplement F (Pregnant Women, etc.) and Supplement G (Adults Who Are or May be Unable to Consent to Research). The IRB will review the NIH Intramural Clinical Initial Protocol Application in its entirety.

D. In addition to its obligations outlined in other SOPs, including SOPs 14B, 14C,14D,14E and 14F, the IRB:

1. Ensures that the PI identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides the justification for their inclusion in the study.

2. Ensures that the PI provides appropriate safeguards to protect the subject's rights and welfare.

3. Shall give consideration to, and require as needed, the inclusion, either as members or *ad hoc* consultants, of individuals who have experience with the vulnerable populations involved in the proposed research. (Prisoner representatives must be IRB members, not consultants.)

4. Reviews the PI's justifications for including vulnerable populations in the proposed research.

5. Ensures that additional safeguards have been included in the proposed research to protect the rights and welfare of vulnerable subjects, as needed, and assesses the adequacy of additional protections for vulnerable populations provided by the PI.

6. Evaluates the proposed plan for consent and, as needed, assent of the specific vulnerable populations involved.

7. Evaluates the proposed research to determine the need for additional safety monitoring.

14A.5 Procedures for the Continuing Review of a Research Study Involving Vulnerable Subjects

NIH IRBs will conduct continuing reviews consistent with SOP 9. When vulnerable subjects are involved they will also:

A. Review information provided by the PI on the number and types of vulnerable subjects enrolled.

B. Determine whether the protections for vulnerable subjects continue to be adequate.

14A.6 Procedures for Amendments to an IRB-Approved Research Study Involving Vulnerable Subjects

NIH IRBs will review amendments consistent with SOP 10. When the amendment concerns the inclusion of vulnerable subjects, or the proposed change/s will impact vulnerable subjects enrolled on the study, the IRB will:

A. Review existing safeguards to protect the rights and welfare of vulnerable subjects in the protocol to ensure that they continue to be adequate.

B. Ensure that additional safeguards, if required, are included in the study to protect the rights and welfare of these subjects.

C. Determine whether current or past subjects must be informed of the amendment and, if so, how they will be informed (verbally and/or in writing). Current and past subjects must be notified if the study amendment affects their safety and welfare, and current subjects re-consented if the amendment changes future clinical study procedures.

These procedures will be undertaken in addition to those outlined in **section 14.A.4.C** above.

SOP 14B – Research Involving Pregnant Women, Human Fetuses and Neonates
Version 3, 2-25-2016

14B.2 Policy

This SOP incorporates protections required by the NIH Human Research Protection Program (HRPP) as set forth by Federal regulatory requirements at 45 CFR 46, Subpart B - Research Involving Pregnant Women, Human Fetuses and Neonates (**Appendix A** in SOP 14B).

The exemptions at 45 CFR 46.101(b)(1) through (6) may apply to research involving pregnant women, human fetuses, and neonates (also see SOP 6).

In addition to other responsibilities assigned to Institutional Review Boards (IRBs) under 45 CFR 46 and the relevant SOPs, each IRB shall review research covered by Subpart B and approve only research that satisfies the conditions of all applicable sections of this Subpart and the other applicable Subparts of 45 CFR 46.

In limited circumstances, Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) regulations allow for exception(s) from informed

consent requirements for emergency research, but this waiver is not available for research involving pregnant women, human fetuses and neonates (see SOP 12 and SOP 15).

14B.5 Regulatory Criteria for Research Involving Pregnant Women or Fetuses

Pregnant women or fetuses may be involved in research if all the conditions of 45 CFR 46.204 are met (see 45 CFR 46.204 for more information on the applicable criteria.) For pregnant children (as defined in 46 CFR 46.402(a)) and considered minors by applicable law, Subpart D and SOP 14D, should also be followed.

14B.6 Regulatory Criteria for Research Involving Neonates

A. **Neonates of Uncertain Viability and Nonviable Neonates:** May be involved in research if all the conditions of 45 CFR 46.205(a) are met (see 45 CFR 46.205(a) for more information on the applicable criteria).

B. **Neonates of Uncertain Viability:** Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the additional conditions of 45 CFR 46.205(b) have been met (see 45 CFR 46.205(b) for more information on the applicable criteria).

C. **Nonviable Neonates:** After delivery nonviable neonates may not be involved in research unless all of the additional conditions of 45 CFR 46.205(c) are met (see 45 CFR 46.205(c) for more information on the applicable criteria).

D. **Viable Neonates:** A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of 45 CFR 46 Subparts A and D (45 CFR 46.205(d)) (also see SOP 14D) (see 45 CFR 46.205(d) for more information on the applicable criteria).

14B.7 Regulatory Criteria and NIH Requirements for Research Involving, after Delivery, the Placenta, the Dead Fetus or Fetal Material

Research in this category may only be conducted in accord with 45 CFR 46.206 (see 45 CFR 46.206 for more information on the applicable criteria). Additionally, please also refer to the Office of Intramural Research (OIR) Sourcebook (see **References** in SOP 14B) for NIH policy requirements for the research use of fetal tissue and SOP 5.

14C.2 Policy

Biomedical or behavioral research conducted or supported by the U.S. Department of Health and Human Services (DHHS) shall not involve prisoners as subjects unless the research is specifically authorized within 45 CFR 46 Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects (**Appendix A** in SOP 14C). Research involving prisoners may not be initiated or continued until there is both Institutional Review Board (IRB) approval and Office for Human Research Protections (OHRP) approval. This SOP sets forth additional protections required by the NIH's Human Research Protection Program (HRPP) for research involving prisoners as required by 45 CFR 46 Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects. The requirements of this SOP are in addition to those imposed under other subparts of 45 CFR 46 and other relevant SOPs.

A. Informed consent can be waived or altered in research involving prisoners only in accordance with applicable regulations. However, even if informed consent is waived or altered, subpart C of 45 CFR Part 46 still requires that the subjects be clearly informed in advance that participation in the research will have no effect on their parole, if such notification is relevant. (45 CFR 46.305(a)(6)).

B. Secretarial waiver of informed consent in certain emergency research is not available for research involving prisoners (see SOP 12).

C. At NIH, expedited IRB review is not permitted for research involving prisoners as subjects.

D. The exemptions at 45 CFR 46.101(b) cannot be applied to research involving prisoners.

14C.5 IRB Requirements

14C.5.1 Additional Requirements for the Composition of the IRB

In addition to satisfying the general requirements for NIH IRB membership under 45 CFR 46.107 (see SOP 2 and SOP 14A), when reviewing any proposed or ongoing research (e.g., at initial review, continuing review, amendments or unanticipated problems) involving prisoners, the following specific requirements also apply.

A. A majority of the NIH IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership to the IRB. (45 CFR 46.304(a)).

B. At least one member of the NIH IRB must be a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement. (45 CFR 46.304(b)). The prisoner representative is present at the meeting when research on prisoners is reviewed.

C. Any change in the IRB roster by the addition of a prisoner/prisoner representative must be reported to OHRP through the Office of Human Subjects Research Protection (OHSRP) in accordance with 45 CFR 46.103(b)(3).

D. The prisoner/prisoner representative counts towards the quorum only when he or she is in attendance and reviewing studies covered by subpart C.

14C.5.2 Role and Responsibilities of the Prisoner Representative

A. The prisoner representative must be a voting member of the IRB.

1. The prisoner representative must review research involving prisoners consistent with **14C.5.1** and **14C 5.3**, and like all IRB members, will focus on the applicable requirements in Subpart C or equivalent protections.

2. The prisoner representative must receive all review materials pertaining to the research (even if there is a primary reviewer).

B. The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved.

1. The prisoner representative may attend the meeting by phone, video-conference, or webinar, as long as the representative is able to participate in the meeting as if present in person.

C. The prisoner representative must present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed (See **14C.7**, below, for the description of the four categories of permitted research with prisoners).

14C.5.3 Additional Duties of NIH IRBS Reviewing Research Involving Prisoners

In addition to all other responsibilities prescribed for IRBs under 45 CFR 46 Subpart C, an NIH IRB will review research involving prisoners and approve such research only if it finds that the research under review falls into one of the four categories of research permissible under 45 CFR 46.306(a)2 and complies with 45 CFR 46.305. (See 45 CFR 46.305 and .306 for more information.)

14C.7 Permitted Research Involving Prisoners

When a Principal Investigator (PI) prepares a protocol that anticipates the enrollment of prisoners he/she must include information that will allow the IRB to carry out the risk analysis set forth below and he/she can use as guidance the information described in **Supplement I – Research Involving Prisoners as Subjects** (**Appendix B** in SOP 14C).

The IRB will review research involving prisoners and approve such research only if it finds that the research under review falls into one of the four following categories:

A. Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.

B. Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.

C. Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) (see 45 CFR 46.306(a)(2)(iii) for additional procedural requirements).

D. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, see 45 CFR 46.306(a)(2)(iv) for additional procedural requirements.

14C.9.2 Actions Required if an Ongoing Protocol Was Not Reviewed Under the Requirements of this SOP (Subpart C, 45 CFR 46) and an Already-Enrolled Research Subject Becomes a Prisoner during the Course of the Study

A. The PI must promptly notify the IRB and NIH's OHSRP.

B. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must stop immediately until the requirements of 45 CFR 46 subpart C have been satisfied for the relevant protocol, except as noted in C, below.

C. The one OHRP exception is that in special circumstances in which the PI asserts that it is in the best interests of the subject to remain in the research while incarcerated, the IRB Chair may determine that the subject may continue to participate in the research until the requirement of subpart C (and this SOP) are satisfied.

D. Upon receipt of notification that a previously enrolled research subject has become a prisoner, the IRB must promptly re-review the protocol in accordance with the requirements of subpart C and this SOP if the investigator wishes to have the prisoner subject continue to participate in the research.

E. The NIH, through OHSRP, will send a certification to OHRP (see **14C.6.A** above). Research may not resume with the prisoner until OHRP provides a written authorization.

SOP 14D – Research Involving Children
Version 4, 5-4-2016

14D.2 Policy

A. The NIH HRPP follows the requirements of this SOP which are consistent with Federal Regulations for the Protection of Human Subjects (45 CFR 46) Subpart D (see **Appendix A** in SOP 14D). For the applicable requirements of the Food and Drug Administration (FDA), see 21 CFR 50, Subpart D – Additional Safeguards for Children in Clinical Investigations (see **References** in SOP 14D). The requirements of this SOP are in addition to those imposed under other subparts of 45 CFR 46 and other relevant SOPs.

B. Children must be included in research unless there are scientific justifications and/or ethical reasons not to include them (see **14D.5.1.B**, below).

C. There are exemptions that may not apply to research involving children. The exemption for research involving the use of educational tests (45 CFR 46.101(b)(2)) is narrowed in scope when applied to involving children (for more information, see SOP 6). The other five exemptions found at 46.101(b) apply to research involving children in the same way that they apply to research involving adults.

D. The Secretarial waiver of informed consent in certain emergency research may be applicable to research involving children (see SOP 12).

14D.5 Responsibilities of NIH IRBs Regarding Review of Research Involving Children

14D.5.1 Approval of Research Involving Children

An IRB may approve research involving children only if it has determined and documented in its minutes that:

A. The research is scientifically sound and significant.

B. In keeping with ethical guidelines on research involving children, when appropriate, earlier studies have been conducted first on animals and adult humans, and then on older children before involving younger children and infants. Investigators must provide and IRBs are responsible for approving ethical and scientific justifications for recruiting children within the age range stipulated in the protocol.

C. Risks to children are minimized using the safest procedures available consistent with sound research design and, whenever feasible, using procedures performed for diagnostic or treatment purposes.

D. Adequate provisions are made to protect the privacy of children and their parents or guardians, and to maintain the confidentiality of data.

E. Subjects will be selected in an equitable manner; and

F. The conditions of all other applicable sections of this SOP are met.

14D.5.2 Allowable Categories of Research

A. The DHHS federal regulations permit four categories of research involving children:

1. Category 1. 45 CFR 46.404, Research not involving greater than minimal risk

2. Category 2. 45 CFR 46.405, Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

3. Category 3. 45 CFR 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

4. Category 4. 45 CFR 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.

B. Each category imposes special requirements upon the IRB's review of any study involving children. The IRB is responsible for determining into which of the four categories of permitted research the study belongs and it must document its rationale for this decision in the minutes and IRB records. The IRB should consult the PI in making this determination.

C. In the case of Category 4 (45 CFR 46.407), a determination by the Secretary, DHHS is required. The IRB will forward the approved research protocol to the Director, Office of Human Subjects Research Protections (OHSRP) who will present it to the Deputy Director of Intramural Research (DDIR) (the Institutional Official) or designee for approval. Upon approval by the DDIR, OHSRP will forward the protocol to the Office for Human Research Protections (OHRP) for review by the Secretary, DHHS and, if appropriate, the Commissioner, FDA per 21 CFR 50.54.

D. For FDA requirements regarding research in children see 21 CFR 50, Subpart D, Additional Safeguards for Children in Clinical Investigations (see **References** in SOP 14D).

14D.6 Responsibilities of NIH PIs and IRBs Regarding Requirements for Obtaining and Documenting Permission by Parents or Guardians

14D.6.1 Obtaining or Waiving Parental Permission

When reviewing research involving children, the IRB must ensure, that adequate provisions have been made for soliciting the permission of each child's parent or guardian in accordance with, and to the extent that is required, by 45 CFR 46.116, and as described in SOP 12. Additional requirements for obtaining permission are described in 45 CFR 46.408(b).

When parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research conducted under categories 1 and 2 (see **14D.5.2** above) and the IRB should document this finding. IRBs should also document if permission from both parents is required. Where research is conducted under categories 3 and 4 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

In cases where parents share joint legal custody for medical decision-making of a child (e.g., by a custody agreement or court order), both parents must give their permission regardless of the risk level of the research. Exceptions may include if one parent has since died, become incompetent, or is not reasonably available (e.g., in prison). Guidance from the Office of the General Counsel should be sought if you have questions about the legal custody of a child or the availability of a parent.

If an IRB chooses to waive the consent requirements of Subpart A and 45 CFR 46.408(b), the requirements of 45 CFR 46.408(c) must be followed.

14D.7.2 IRB Responsibilities [Regarding Requirements for Obtaining and Documenting Assent by Children]

A. The IRB shall determine that adequate provisions are made for:

1. Soliciting the assent of children when the IRB determines that children are capable of assent, see **14D.7.2.B**, below, and **Appendix C** in SOP 14D. This appendix is based on the Medical Administrative Series 92-5 “Research Involving Children and Children’s Assent in Research” (see **References** in SOP 14D). And ensuring that children have not withdrawn assent.

2. A child’s failure to assent should be binding unless the research holds out a prospect of direct benefit that is important to the health and wellbeing of the child and that is available only in the context of research and the IRB has determined, consistent with regulations, that assent is not required.

3. Monitoring the solicitation of assent when appropriate.

4. Re-consenting minors when they reach the age of consent, if applicable. See **14D.8** for guidance.

B. The IRB will determine and document whether assent is a requirement of all, some, or none of the children on a protocol. When assent is not a requirement for some children, the IRB will document which children are not required to assent.

C. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular study, or for each child, as the IRB deems appropriate.

1. The assent of child research subjects is not a necessary condition for proceeding with the research in the circumstances in which the IRB determines that (i) some or all of the children's capabilities are so limited that they cannot reasonably be consulted, or (ii) the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research.

2. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement in circumstances in which consent may be waived in accordance with 45 CFR 46.116 and 45 CFR 46.408(a) (see SOP 12).

14D.7.3 Documentation of Assent

A. If an IRB determines that assent will be obtained, it shall determine whether, and how, it shall be documented (46 CFR 46.408(e)). If assent is obtained verbally, this should be documented on the research consent form signed by the parents/guardians.

B. When a written assent document is used, the signatures of the child and investigator should be documented on the assent form. The signatures of the parent(s)/guardian(s), investigator and a witness (when applicable) will be documented on the consent form (see SOP 12).

14D.8 Responsibilities of NIH PIs and IRBs Regarding Consenting Minors Who Reach the Age of Consent while on a Research Study, Including Those Who Are or May Be Unable to Consent

A. PIs should obtain consent from minors previously enrolled on protocols once the minors reach the age of consent[2] pursuant to the procedures outlined in SOP 12. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject.

B. The PI should seek and obtain the legally effective informed consent of the now-adult subject unless the IRB has determined and documented that the requirements for obtaining informed consent can be waived under 45 CFR 46.116 (d).

C. The PI should seek and obtain the legally effective informed consent of the now-adult subject even if the research does not involve any ongoing interactions or interventions with the subject, but continues to meet the regulatory definition of "human subjects research" (e.g., it involves the continued analysis of identifiable specimens or data). In these circumstances, if appropriate, the IRB may consider a waiver under 45 CFR 46.116 (d).

D. If applicable, PIs should outline in their protocols how consent will be obtained when minor subjects reach the age of consent to ensure a smooth transition for subjects and their families. IRBs should review these provisions to ensure that they are adequate. Consideration should be given to forewarning subjects and their families at the time of enrollment that there will be a need to consent the minor subject on reaching the age of consent. This information can prevent a situation where parents might feel that the act of consenting is questioning a prior decision to enroll their child in a study.

E. In instances where an older minor subject might be cognitively impaired and is likely to be unable to provide consent as an adult, an advanced discussion of this possibility may help prepare parent(s)/ guardian(s) for next steps (e.g., whether they can act as a legally authorized representative in the context of NIH intramural research when the minor becomes an adult) (see SOP 14E).

F. For now-adult subjects who are unable to provide on-going consent, the PI should follow the guidance outlined in SOP 14E, unless the IRB has waived the requirement for informed consent.

[2] For the purpose of consent at the NIH Clinical Center (CC), an adult is anyone 18 years or older or an emancipated minor (such as a minor who is married or a parent). At non-CC NIH sites applicable local, state or foreign law is followed in the absence of applicable U.S. Federal law.

14D.9 Children Who Are Wards

A. Children who are wards of the State or any other agency, institution, or entity can be included in approved Category 3 (45 CFR 46.406) or Category 4 (45 CFR 46.407) research only if such research is:

   1. Related to their status as wards; or

   2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

B. If the research meets the above condition(s), the IRB must require the appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as an advocate for more than one child.

   The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research. Additionally, the advocate must not be associated in any way (except in the role as an advocate or member of the IRB) with the research, the investigator(s), or the guardian organization. (45 CFR 46.409).

SOP 14E – Research Involving Adults Who Are or May Be Unable to Consent
Version 2, 5-25-2016

14E.2 Policy

This SOP sets forth additional protections required by the NIH's Human Research Protection Program (HRPP) for NIH subjects who participate in research activities led by NIH investigators. Such research takes place mainly at NIH sites (i.e., NIH Clinical Center (CC) NIDA Baltimore, NIDDK Arizona, NIEHS North Carolina, NIA Baltimore) and is usually reviewed by an NIH IRB, however the research could occur at another location and NIH could rely on an outside IRB.

14E.6 NIH IRB Responsibilities

14E.6.1 Review Requirements

When reviewing research protocols involving adults who are or may be unable to consent, the NIH IRB will:

A. Ensure there is a compelling justification for including adults who cannot consent (e.g., the research question cannot be answered by enrolling only adults who can consent; participation offers the potential for important clinical benefit).

B. Ensure that the procedures for evaluating an adult's ability to provide initial and on-going consent are appropriate.

C. Stipulate that the consent of an appropriate LAR will be obtained consistent with this policy.

D. Assess and document the risks and prospect of direct benefit (if any) for adults unable to consent.

E. Determine and document the category of research as specified in **14E.6.2** below.

F. If applicable, ensure that the procedures for obtaining assent and respecting dissent are appropriate. If an IRB determines that assent will be obtained, it shall determine whether, and how (written, oral, or by other means) it shall be documented (see SOP 12), and

G. Determine whether any additional safeguards will be used (e.g., consent monitoring).

H. When an NIH IRB is serving as an IRB of record and the protocol involves adults who are or may be unable to consent, it should obtain information about how the consent process will be conducted if this vulnerable group of subjects is to be enrolled outside of the NIH CC. This information should be evaluated by the IRB as part of its local context considerations. See SOP 20B.

14E.6.2 NIH IRB Determination of Allowable Categories of Research

NIH IRBs may approve the participation of adults who are or may be unable to consent in research that falls into one of the following categories only:

Category A - Research not involving greater than minimal risk.

Category B - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Category C - Research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects.

Category D - Research not otherwise approvable under categories A-C in this policy.

1. In order to approve research in this category an NIH IRB must, in addition to fulfilling the other requirements of this SOP, determine and document that the knowledge to be obtained:

   i. is of vital importance;

   ii. cannot reasonably be obtained by studying only adults who can consent; and

   iii. cannot be obtained in a way that poses less risk.

2. The IRB must also identify a person(s) (ACAT at the CC) independent of the research team who will assess the appropriateness of the LAR to consent on behalf of the participant. See **14E.7.2** below.

3. Additional review shall be conducted by the NIH Deputy Director for Intramural Research (DDIR) who will convene an independent panel of NIH employees with appropriate subject matter expertise and no conflicts. Conflicts may include but are not limited to: involvement in the development, scientific review, or implementation of the protocol under review; having a direct reporting relationship with the PI; and/or serving as a member of the IRB of record. The panel will provide to the DDIR a written determination regarding the following, whether:

   i. 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;

   ii. the risks of the study are not excessive; and

   iii. additional conditions or protections are needed, e.g., consent monitoring.

The DDIR can concur with the IRB's approval and may allow the conduct of the research or may disapprove implementing the IRB-approved research.

SOP 14F – Research Involving NIH Staff as Subjects
Version 3, 5-26-2016

14F.2 Policy

NIH staff and members of their immediate families may participate in NIH intramural research unless prohibited by their Institute or Center (IC), or excluded by the criteria of the protocol in which they want to enroll. Such research must be conducted consistent with the *Guidelines for the Inclusion of Staff in NIH Intramural Research Studies (March, 2012)* (**Appendix A** in SOP 14F) and the requirements of NIH Policy Manual 2300-630-3 – *Leave Policy for NIH Employees Participating in NIH Medical Research Studies https://oma1.od.nih.gov/manualchapters/person/2300-630-3/* **(Appendix B** in SOP 14F**)**

14F.4.1 Responsibilities of the IRB

Where enrollment of NIH staff is anticipated on an NIH protocol, the Institutional Review Board (IRB) must approve their participation with adequate protections based on the level of risk. If the enrollment of NIH staff is anticipated in research taking place within their own branch, section, or unit; or that is being conducted by any of their direct supervisors, NIH staff may participate in the study when the research outcomes are unlikely to be influenced by the inclusion of staff.

14F.4.2 Responsibilities of the Principal Investigator

B. All protocols should include the following safeguards when enrollment of NIH staff is anticipated:

3. Information specifically on compensation to staff in accordance with NIH policy, see **Appendix B** in SOP 14F.

14F.5 Considerations When Enrollment of NIH Staff Is Not Anticipated and There Is No Prospect of Direct Benefit

A. When NIH staff enrollment was not anticipated in an approved protocol and a PI becomes aware that a staff member wants to enroll in a study that has no prospect of direct benefit, the PI is required by this policy to amend the protocol and obtain IRB approval for staff participation in accordance with this policy.

14F.7 Considerations When a PI or AI Wishes to Enroll in Their Own Study

The enrollment of a PI or AI in his or her own study is not specifically prohibited by NIH, unless by IC policy, but must be independently considered, on a case-by-case basis, by the IRB. Investigators should explain why they want to participate in the protocol as well as outline measures that will be taken to manage possible bias, obtain their informed consent, and manage privacy and confidentiality. The IRB may seek additional advice from Bioethics.

SOP 22 – Research Subject Information and Services and Research-related Complaints from Research Subjects
Version 2, 8-13-2015

22.2 Policy

The NIH's human research protection program (HRPP) has procedures in place to provide information and services to research subjects. The HRPP also ensures that complaints about participation in research are given serious consideration and that efforts are made to identify and resolve such complaints.

22.4.2 Lodging Complaints

A. Research subjects may bring their problems or complaints *regarding their participation in research* to the attention of Principal and/or Associate Investigators (PIs or AIs) or other health care/research staff (e.g., nurses, social workers); OHSRP staff; the NIH IRB Chair and/or IC or other NIH officials. In addition, at the CC, subjects may contact the Department of Bioethics and/or the CC Ethics Committee, and the CC Patient Representative. At non-CC sites, complaints also may be referred to an IC Compliance Office.

B. Issues or complaints related to the quality of clinical care and/or patient safety related concerns at the CC should be directed to the Office of the Deputy Director for Clinical Care (DDCC) or to comparable persons/entities for research conducted at non-CC NIH sites.

C. Complaints that deal with concerns unrelated to research or patient safety/clinical quality, e.g., quality of food, parking problems, etc., are referred to appropriate entities such as the CC Office of the Chief Operating Officer, the CC Department of Social Work and/or the CC Patient Representative or to comparable persons/entities for research conducted at non-CC NIH sites.

22.4.3 Documenting Complaints

Complaints, written or verbal (including telephone complaints) will be documented and kept on file by the recipient (e.g., the PI, the Patient Representative) and in the relevant receiving office (e.g., the IRB administrative office, the OHSRP, the Office of the DDCC, the IC Compliance Office) consistent with applicable laws for privacy. If a complaint

related to research participation is received initially by OHSRP, the appropriate IRB Chair and the PI of the relevant protocol will be notified, as appropriate.

A. Generally, the following information will be documented as applicable:

    1. Subject's (or complainant's) name, address, and phone number, if provided

    2. Protocol title/number and the name of the PI

    3. Date(s) of the incident if known, and

    4. An explanation of the concern, complaint, or question

B. Anonymous reports are accepted. However, the person receiving the complaint may need to advise the complainant that the inability to follow-up to gather more information may hinder an investigation and that the results of an investigation and/or the provision of follow-up information may not be possible (see **Section 22.4.6**).

C. The name of the complainant(s) will be kept confidential to the extent possible. Complainants may be advised that complete confidentiality cannot always be maintained during an investigation.

22.4.4 Investigating Complaints

The following procedures apply to investigating complaints lodged by subjects or others.

A. Attempts are made to respond to complaints as soon as possible. The complainant is informed that the issue will be addressed further, as appropriate, and that a response to him/her will be forthcoming as consistent with **Section 22.4.6**.

B. Complaints from research subjects that cannot be resolved by the research team or Patient Representative will be referred to the appropriate IC Clinical Director or the Director, CC. When appropriate, such as when the complaint may relate to allegations or incidents of non-compliance or to other human subject protection issues (e.g., informed consent, confidentiality, or other topics covered by the NIH HRRP Standard Operating Procedures), the IRB Chair and OHSRP will also be informed.

C. The IRB Chair, IC Compliance Office and OHSRP work collaboratively, with others as appropriate (e.g., Patient Representative, CC Bioethics Department), to investigate the complaint(s) further.

D. **Results of an investigation:** At the conclusion of an investigation, the IRB Chair, OHSRP, and other involved parties as appropriate, will decide if further action is needed:

1. The complaint requires no further action.

2. The complaint is not research-related and is more appropriately handled through non-IRB channels. It will be referred to the appropriate entity (such as the CC Social Work Department).

3. The complaint is research-related and will be forwarded to the appropriate IRB for review.

22.4.5 IRB Review of Findings Related to Complaints

The convened IRB will review issues which meet the criterion under **Section 22.4.4.C.3**, above. It will take appropriate action to ensure the safety and welfare of human research subjects. These actions may involve but are not limited to:

A. Modifying the research protocol and/or consent document(s)

B. Educational measures for the researcher or research team

C. Suspending or terminating IRB approval for some/all of the PIs studies

D. Informing other IC or NIH officials as appropriate

22.4.6 Communication of the Results of an Investigation to the Complainant

Unless the complaint is anonymous, complainants will be notified, when appropriate, by OHSRP or the IRB Chair of the outcome of the investigation conducted by OHSRP and/or the IRB Chair/IC Compliance Office. This communication will be consistent with the Privacy Act and other applicable laws and policy. In some instances, the complainant may simply be told that the matter is being investigated and no further information will be forthcoming.

22.5 Communication about Research Subject Complaints Within the NIH's HRPP

In order to promote open communication about research subject complaints in the CC, the Director of OHSRP, the CC Patient Representative and the Director of CC Department of Bioethics, shall meet as needed to review issues related to subject complaints. Non-CC sites may also arrange for meetings with the IRB Chair, OHSRP, and IC Compliance Office to review issues related to subject complaints.

CHAPTER 4: FOOD AND DRUG ADMINISTRATION REQUIREMENTS

15.2 Policy

NIH researchers will conduct research that involves test articles* and human subjects* (i.e., clinical investigations*, in accordance with relevant FDA and Department of Health and Human Services (DHHS) regulatory requirements and consistent with the Guideline for Good Clinical Practice* (GCP) as adapted by the FDA (**References** in SOP 15). Additional procedures specific to FDA-regulated IND* and IDE* research are detailed under SOP 15A and SOP 15B. In their review of this research, NIH IRBs will comply with the applicable requirements set forth in FDA regulations, 21 CFR part 56 (see **References** in SOP 15) and those of DHHS, 45 CFR 46 (**References** in SOP 15). For a comparison between the FDA and DHHS regulations, see **References** in SOP 15.

15.3.1 General Responsibilities and Communication with the IRB

A. **General responsibilities: Investigators*** will carry out clinical investigation of drugs or medical devices in accordance with FDA regulations (21 CFR parts 312 and 812) and guidelines (see FDA Guidance Documents and Information Sheets regarding good clinical practice and the conduct of clinical trials (**References** in SOP 15). Principal Investigators (PIs) will also adhere to specific IRB requirements, NIH Standard Operating Procedures (SOPs) and any NIH Institute-specific procedures or requirements.

    1. The term Principal Investigator is defined in SOP 19. A PI will also be an "investigator" under FDA regulations. Therefore, in this SOP the terms are used interchangeably.

B. Prospective IRB review and approval:

    1. Before research begins, the PI will obtain IRB approval of the protocol, any consent document(s), and any other information to be provided to subjects, consistent with SOP 7.

    2. At initial submission, the PI will complete the NIH Intramural Clinical Protocol Application form and, if the research involves investigational drugs or devices, inform the IRB whether the research requires an IND (see SOP 15A) or IDE (see SOP 15B). If the research question involves investigational drugs or devices, or the use of commercially available products for an off-label use and there is no IND in effect or no approved IDE, the PI must provide a rationale why such an application is not required at the time of IRB submission. If no IND or IDE is required, and if the appropriate criteria for expedited review are met as addressed in SOP 7A, the IRB Chair will decide if the protocol is eligible for

consideration under the expedited review process or if it should be sent for full Board review. If an IND or IDE is required, in addition to the IND/IDE number, the PI will provide the IRB with written communication indicating assignment of the IND/IDE number as part of the initial application for review by the convened IRB. See SOP 15A for examples of such documentation.

Research may not begin until a valid IND/IDE is in effect. An IND/IDE goes into effect 1) 30 days after the FDA receives the IND/IDE, unless the FDA notifies the sponsor that the investigations described in the IND/IDE are subject to a clinical hold under 21 CFR 312.42 (IND's) or 21 CFR 812.30 (a)(1) (IDE's); or 2) an earlier notification that the clinical investigations in the IND may begin (21 CFR 312.40 (b)) or the FDA approves, by order, an IDE for the investigation (812.30 (a)(2)). If the IND/ IDE application has not been submitted to the FDA at the time of the initial IRB protocol submission, the IRB will stipulate that documentation of a valid IND/IDE (see criteria above) must be provided to the IRB prior to full approval. The IRB staff will be responsible for confirming that a valid IND/IDE is in effect prior to full approval of the protocol. If there is any question about the documentation, it will be referred to the Chair for review

3. **Investigator's Brochure*:** The PI will provide any extant Investigator's Brochure (or alternative communication) in the submission of the protocol to the IRB. If the PI has not submitted the IB at the time of the initial application, the IRB must defer approval until the IB has been submitted and reviewed by the IRB.

4. If the Investigator's Brochure is updated during the trial, the PI will provide the updated version to the IRB.

5. **Amendments to previously approved research:** The PI will obtain prospective IRB review and approval of proposed amendments to previously approved research consistent with SOP 10.

6. **Continuing review:** The PI is responsible for submitting continuing reviews of research protocols consistent with SOP 9.

C. **Reporting unanticipated problems, including adverse events* and unanticipated adverse device effects* to the IRB:** The PI will promptly report to the IRB any unanticipated problems involving risks to subjects and others and any unanticipated adverse device effects (see FDA regulations 21 CFR 312.66 and 21 CFR 812.150(a)(1), and SOP 16).

D. **Responsibilities of a PI who is also a Sponsor-Investigator*:** A sponsor-investigator is defined as an "individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject." When the PI is also the sponsor-investigator, the PI is responsible for assuring the IRB that

s/he has reviewed the "Information for Sponsor-Investigators Submitting Investigational New Drug Applications" (**References** in SOP 15) or information regarding the IDE Approval Process (**References** in SOP 15) and will comply with the regulatory responsibilities of a sponsor and an investigator.

Sponsors* are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND/IDE, maintaining an effective IND/IDE with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described in 21 CFR 312 Subpart D and 21 CFR 812 Subpart C.

15.3.7. Informed Consent of Research Subjects

A. **Informed Consent Document:** In addition to satisfying FDA requirements and the requirements in SOP 12, the consent document for applicable FDA-regulated clinical trials must include the following statement: "If this trial is an applicable clinical trial, the following statement applies: A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time." (21 CFR 50.25(c))

B. **Non-therapeutic research*:** FDA-regulated research may include non-therapeutic trials (trials in which there is no anticipated direct clinical benefit to the subject). Such research may be conducted at the NIH in the following circumstances:
   1. With the written informed consent of the subject, or
   2. With the written informed consent of a legally authorized representative provided the following conditions are fulfilled:
      a. The objectives of the trial cannot be met by means of a trial involving subjects who can give their own informed consent.
      b. The foreseeable risks to the subjects are low.
      c. The negative impact on the subject's well-being is minimized and low.
      d. The trial is not prohibited by law.
      e. The approval of the IRB is expressly sought on the inclusion of such subjects, and the IRB's written approval covers this aspect. In the NIH IRB review of this research, the PI and IRB will follow the requirements of SOP 14A.

C. Informed consent requirements for emergency research:
   1. **General considerations:** An NIH PI may conduct research under the requirements of 21 CFR 50.24 (see **References** in SOP 15), provided it is also consistent with the requirements of 45 CFR 46.
   2. For more information regarding emergency use of investigational drugs, see SOP 15A and for devices, see SOP 15B.

D. Waiver of requirement to document the consent process:

1. Unless criteria for an exception from the general requirements for consent (21 CFR 50.23) or an exception for emergency research are met (21 CFR 50.24), no investigator may involve a human being as a subject in research covered by the FDA regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. Unless there is an exception (21 CFR 56.109(c)), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent.
2. The IRB may waive the requirement to have a subject or subject's legally authorized representative sign a written consent form in certain circumstances (see 21 CFR 59.109(c)(1) or by determining that the regulatory criteria within 21 CFR 50.24 are met (see 21 CFR 56.109(c)(2)).
3. When the IRB considers waiving the requirement to obtain written documentation of the consent process, the IRB reviews a written description of the information that will be provided either verbally or in writing to participants. This may be a script or a statement about what information will be conveyed.

E. Informed Consent for in Vitro Diagnostic Devices Using Leftover Human Specimens that are not Individually Identifiable

When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects. However, in its guidance for sponsors, IRB's, investigators and FDA staff, issued April, 2006 (*Guidance on Informed Consent for In Vitro Diagnostic Devices Using Leftover Human Specimens that are not Individually Identifiable)*, FDA indicated the following: "FDA does not intend to object to the use, without informed consent, of leftover human specimens -- remnants of specimens collected for routine clinical care or analysis that would otherwise have been discarded -- in investigations that meet the criteria for exemption from the Investigational Device Exemptions (IDE) regulation at 21 CFR 812.2(c)(3), as long as subject privacy is protected by using only specimens that are not individually identifiable. FDA also intends to include in this policy specimens obtained from specimen repositories and specimens that are left over from specimens previously collected for other unrelated research, as long as these specimens are not individually identifiable."

15.3.12 Premature Termination or Suspension of a Trial

A. **By the PI:** If the PI terminates, or suspends a trial without prior agreement of the sponsor, the PI will inform the IRB and the sponsor. Communication from the PI to the IRB and the sponsor will include a detailed written explanation of the termination or suspension.

B. **By the sponsor:** If the sponsor terminates or suspends a trial, the PI should promptly inform the IRB and provide it with a detailed written explanation of the termination or suspension.

C. **By an IRB:** If an NIH IRB terminates or suspends its approval of a trial the PI will inform the sponsor. The IRB will report its actions to the investigator, NIH Institutional officials, and OHSRP. OHSRP will report termination or suspension of a trial to the FDA (and OHRP as applicable) consistent with SOP 24 and in accordance with FDA regulations (21 CFR 56.113).

D. **Informing research participants about suspension/termination:** If the trial is terminated prematurely or suspended for any reason, the PI will promptly inform the trial subjects, and should assure appropriate therapy and follow-up for the subjects, according to procedures in SOP 11.

E. **Informing regulatory authority(ies):** Where required by the applicable regulatory requirement(s), the PI must inform the regulatory authority(ies).

15.4 Responsibilities of the IRB When Reviewing Research Involving INDs and/or IDEs

15.4.1 Review of IND/IDE Status

A. The IRB administrative staff, in collaboration with the IRB Chair, will review the documents provided by the PI (see SOP 15A and SOP 15B) and confirm whether the research requires an IND/IDE and that there is appropriate supporting documentation. If the PI has not submitted the appropriate IND/IDE documentation at the time of the initial application and the IRB determines that an IND or IDE is needed, or that a determination regarding need for an IND/IDE by the FDA is indicated, the IRB will stipulate that the research may not begin until the IRB staff has confirmed receipt of the appropriate FDA IND/IDE documentation. If the PI has not submitted the IB (or alternative communication) at the time of the initial application, the IRB must defer approval until the IB has been submitted and reviewed by the IRB.

15.4.2 General Considerations for IRB Review of Research Involving INDs or IDEs

A. The IRB will review the research protocol in accordance with applicable DHHS regulations (see SOP 8), and FDA regulations (see 21 CFR part 56, **References** in SOP 15, for FDA regulations related to IRBs).

B. If the IRB does not have the necessary expertise to review the specific research activity (see 21 CFR 56.107 for FDA requirements related to IRB membership), additional consultation will be sought consistent with SOP 2.

C. The IRB will review proposed advertising to ensure that advertisements do none of the following:

1. Make claims, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device;

2. Use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational;

3. Allow “compensation" for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

D. Additional responsibilities and procedures for IRB review of INDs are detailed in SOP 15A and for review of IDEs in SOP 15B.

15.4.3 FDA Inspections and Audits of NIH IRBS

A. IRBs must make records available for FDA inspection in accordance with 21 CFR 56.115(b), and 812.145. NIH IRBs that are informed of an FDA inspection or audit should immediately notify their Clinical Director(s) and the Director, OHSRP.

1. Any written responses by an NIH IRB Chair to the FDA must be submitted for approval to the Clinical Director and the Director, OHSRP at least two days before the Chair’s submission to the FDA.

SOP 15A – Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products)
Version 4, 2-24-2106

15A.3 Policy

Investigations involving **investigational drugs*** must be conducted in accordance with applicable FDA regulations, including the investigational new drug regulations at 21 CFR Part 312 (see **References** in SOP 15A). Such investigations should also be conducted consistent with GCP (**References** in SOP 15A) and with the policies contained in SOP 15.

15A.7 Exception from Informed Consent Requirements for Emergency Research

These requirements are found in 21 CFR 50.24 (see **References** in SOP 15A).

FDA regulations related to exception from informed consent for emergency research (21 CFR 50.24.) are located in Appendix D in SOP 15A. This research must also comply with the requirements of 45 CFR 46, if applicable.

15A.8 Expanded Access to Investigational Drugs for Treatment Use, including Emergency IND

15A.8.1 General Considerations and Definitions

A. **General Considerations:** FDA's regulations at 21 CFR 312.300-312.320 (see **References** in SOP 15A) contain the requirements for the use of investigational new drugs (and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition.[3] The aim of these regulations is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition. These regulations contain criteria, submission requirements, and safeguards applicable:

1. to all expanded access uses (21 CFR 312.305),

2. when an investigational drug is to be used for the treatment of an individual patient, including for **emergency uses*** (21 CFR 312.310),

3. when an investigational drug is to be used in the treatment of an "intermediate-size" patient population (21 CFR 312.315), and

4. when an investigational drug is to be used for widespread treatment use (21 CFR 312.320).

B. **Definitions:** For the purposes of the regulations regarding expanded access to investigational drugs (21 CFR 312.300-320), the following definitions apply:

1. Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment, 21 CFR 312.300(b).

[3] Generally expanded access activities, including expanded access program activity for emergency uses, are for treatment purposes only and therefore are not considered human subjects research under 45 CFR 46. If an expanded access activity, including an emergency use, also involves research, then the human subjects protections rules (45 CFR 46) apply. FDA generally requires that data from expanded access uses be reported to it.

2. Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one, 21 CFR 312.300(b).

15A.8.2 Criteria and Safeguards Applicable to All Expanded Access Uses

A. Under 21 CFR 312.305(a), for any expanded access use, including emergency uses, FDA must determine that:

1. The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

2. The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

3. Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

B. 21 CFR 312.305(c) also provides various safeguards for all expanded access uses, including that investigators are responsible for ensuring that expanded access protocols are conducted in accordance with 21 CFR part 50 (FDA's informed consent regulations) and 21 CFR part 56 (FDA's IRB regulations).

15A.8.3 Emergency Use IND for Non-Research Purposes

A. **FDA Regulations in general:** Under 21 CFR 312.310(d), if there is an emergency that requires that an individual patient be treated before a written IND submission to the FDA (also known as an Emergency IND) can be made in accordance with 21 CFR 312.310(b) and 312.305(b), the FDA may authorize the Emergency use IND expanded access use by telephone, facsimile or other means of electronic

submission (for more information see **References** in SOP 15A). In such a case, the licensed physician or sponsor must explain how the expanded access use will meet the requirements of 312.305 and 312.310 and must agree to submit an expanded access submission within 15 working days of the FDA's authorization of the use.

B. Informed consent for emergency use:

For an emergency use and documentation, as with all expanded access uses, the investigator is required to obtain informed consent from the subject or the subject's legally authorized representative in accordance with FDA regulations at 21 CFR part 50 (see 21 CFR 312.305(c)(4)). Circumstances will dictate which one of the following two courses of action will be taken with regard to exception of informed consent for emergency use. 21 CFR 50.23 provides exceptions to the general informed consent requirement for the emergency use of a **test article*** in a single patient (see **References** in SOP 15A), including as follows:

1. Informed consent is not required if both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing that all of the following conditions are met:

   a. The subject is confronted by a life-threatening situation necessitating the use of the test article.

   b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.

   c. Time is not sufficient to obtain consent from the subject's legal representative.

   d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

2. If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and time is not sufficient to obtain an independent physician's determination that the four conditions above apply in advance of using the test article, the clinical investigator should make the determination. In this circumstance, within 5 working days after the use of the article, the investigator must have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

   The documentation required in paragraph (2) or (3) above shall be submitted to

the IRB within 5 working days after the use of the test article (see 21 CFR 50.23(c)). The IRB will review these reports to determine if the circumstances met FDA regulations.

For more information, refer to 21 CFR part 50 (see **References** in SOP 15A).

C. FDA Requirements for IRB Review of Emergency Use INDs

For an Emergency use IND, as with all expanded access uses, an investigator is responsible for ensuring that IRB review is obtained in a manner consistent with the requirements of 21 CFR part 56 (see 21 CFR 312.305(c)(4)). Emergency use of an investigational drug in accordance with 21 CFR 312.310 is exempt from the requirement for prospective IRB review and approval, provided that such use is reported to the IRB within 5 working days (21 CFR 56.104(c)). NIH researchers should also be aware that:

1. FDA regulations require that any subsequent use of the investigational product at the institution be subject to IRB review (21 CFR 56.104(c)).

2. The FDA regulations do not provide for expedited IRB approval in emergency situations (see 21 CFR 56.110).

15A.8.4 NIH Requirements for Emergency INDs

In addition to the FDA requirements for Emergency IND usage above, the NIH has the following requirements:

A. NIH requires that the IRB Chair/designee and the IC Clinical Director/designee sign the “Notification Form: Emergency IND” form. This may be done after seeking approval from the FDA. For more information and to obtain NIH approval for emergency use of an investigational drug, use **Attachment 1** “Notification Form: Emergency IND”.

B. When emergency treatment has ended, the investigator will submit a completion report to the IRB.

15B.2 Policy

Investigations involving investigational devices must be conducted in accordance with applicable FDA regulations, including the investigational medical devices at 21 CFR Part 812 (see **References** in SOP 15B). Such investigations should also be conducted consistent with **FDA Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance (April 1996)*** (FDA GCP) (see **References** in SOP 15B) and with the policies contained in SOP 15. Also see "Device Advice", in **References** in SOP 15B.

15B.5 Responsibilities of the IRB When Reviewing Research Involving IDEs

15B.5.1 Review of Proposed IDE Status

A. The IRB administrative staff, in collaboration with the IRB Chair, will review the documents provided by the PI and confirm whether the research requires an IDE and that there is appropriate supporting documentation. If IDE documentation is not available at the time of the initial protocol submission, the IRB will stipulate that study/amendment approval is contingent on receipt of the appropriate IDE documentation by the IRB (along with the Investigator's Brochure). The IRB staff will confirm that appropriate documentation of the IDE has been received (as defined in section **15B.4.1.C** above).

B. A report of prior investigations should be submitted at the time of the initial application. If this information is not available, the IRB must defer approval until it has been submitted and reviewed by the IRB to adequately assess potential risks to subjects associated with use of the device.

15B.5.2 IRB Review of Research Involving Investigational Devices

A. Significant Risk Devices

1. **Determination of Significant Risk (SR) devices by the FDA:** If the FDA has made an SR determination for the study then the IRB does not make an independent risk determination. The PI will note the FDA's determination in the written protocol and will provide the IRB with the FDA's IDE approval letter.

2. **Determination of Significant Risk (SR) devices by the IRB:** If the FDA has not made a risk determination for the study, the IRB should review the sponsor's proposed risk determination. If the IRB determines that the device used in the study is NSR, then submission of an IDE application to the FDA is not required. If the sponsor has determined that the device used in a study is NSR but the IRB disagrees and determines that the device is SR, the IRB must notify the investigator and, where appropriate, the sponsor (see 21 CFR 812.66, see **References** in SOP 15B). In making this determination of significant risk, the IRB will take into account how the device is used in the study and apply FDA IDE

guidelines. For more information about significant risk and non-significant risk medical device studies see **References** in SOP 15B.

a. If the IRB believes the protocol is a significant risk device study, the IRB may approve the study but the study cannot begin until the FDA approves the IDE or the FDA determines that an IDE is not needed.

b. The IRB will not review studies involving significant risk devices under expedited review procedures.

B. Non-Signification Risk Devices

1. Determination of NSR by the FDA. If the FDA has already made an NSR determination, the IRB does not need to duplicate the effort by making an independent risk determination.

2. Determination of NSR by the IRB:

a. If the FDA has not already made the NSR determination, the IRB should review the sponsor's proposed risk determination. If the IRB determines that the device used in the study is NSR, then submission of an IDE application to the FDA is not required. If the sponsor has determined that the device used in a study is NSR but the IRB disagrees and determines that the device is SR, the IRB must notify the investigator and, where appropriate, the sponsor (see 21 CFR 812.66, see **References** in SOP 15B).

b. If the IRB makes a NSR determination, submission of an IDE application is not required but the study must be conducted in accordance with the abbreviated requirements of IDE regulations (see 21 CFR 812.2(b), see **References** in SOP 15B).

3. FDA considers an NSR device study to have an approved IDE after IRB approval and when sponsors meet the abbreviated requirements at 21 CFR 812.2(b) unless notified under 21 CFR 812.20(a) that approval of an application is required. (See **References** and "Information Sheet Guidance for IRBs, Clinical Investigators", and "Sponsors Frequently Asked Questions About Medical Devices" in SOP 15B). If an IRB finds that an investigational medical device study poses a NSR, the sponsor does not need to submit an IDE to FDA before starting the study.

C. If a sponsor or the IRB needs help in making the SR/NSR determination, it may ask for written guidance from the FDA.

D. The IRB will document its determination regarding device risk in the minutes. The IRB will also notify the PI in writing of its determination and the rationale for the determination.

CHAPTER 5: WORKING WITH SPECIMENS AND DATA

SOP 5 – NIH Research Activities with Human Data/Specimens
Version 2, 9-17-2013

5.2 Policy

NIH seeks to maintain the highest ethical standards when research is conducted with human specimens and data, following 45 CFR 46 requirements, and principles set forth in the Belmont report. The NIH Office of Human Subjects Research Protections (OHSRP) and/or NIH IRBs review research activities with human specimens and/or data, unless those activities are excluded from review by NIH policy. This SOP provides an overview of NIH requirements that pertain to NIH research activities with human specimens and data.

The requirements of this SOP do not apply to activities that involve only specimens and data from the sources set forth in Appendix 1 in SOP 5. Consequently, NIH activities that involve only these specimens and data found in Appendix 1 may proceed without any prior approval from an IRB or OHSRP.

5.4 NIH Policy for Common Categories of Research Activities with Data/Specimens

This SOP and SOP 6 set forth NIH policies and procedures covering the most common categories of research activities with specimens and data. Those categories are set forth below with a reference to SOP sections that contain additional information about NIH policy for that particular research activity.

A. Non-Exempt Research requiring IRB Review:

1. **Prospective collection of specimens and/or data through direct interventions or interactions with subjects or obtaining individually identifiable information for research (Section 5.5):** IRB review is required when NIH researchers prospectively collect data or specimens for non-exempt research through direct interventions or interactions with subjects or when a researcher obtains individually identifiable information for research. This includes obtaining coded data or specimens (with or without the code) collected by others, e.g., a collaborator, through intervention or interaction with human subjects for the same research purpose

2. **Secondary use of Identified or Coded specimens and/or data when NIH researchers can identify the subjects (Section 5.6):** IRB approval is also required for secondary non-exempt research use of specimens and/or data when NIH researchers or members of the research team can identify the subjects, e.g., through direct access to identifiers or when the research team has coded specimens or data with access to the key to the code.

3. **Collaborative Research:** When either party in collaborative research (see SOP 20) is engaged[4] in non-exempt human subjects research, the entire project must be approved by an IRB, either at the NIH and/or by an outside IRB. If the protocol is approved only at an outside IRB, there must be a reliance agreement for NIH to rely on the outside IRB (see SOP 20 A), unless the NIH collaborator will not be receiving any individually identifiable information. If the NIH is not interacting with human subjects or receiving any individually identifiable information during the collaboration, then OHSRP must review the collaboration and make an appropriate determination. Further, an agreement must be in place to ensure that individually identifiable information will not be shared.

5.5 Prospective Collection of Specimens and Data for Research through Direct Intervention or Interaction with Subjects or Non-Exempt Research with Identifiable Private Information

IRB review is required when NIH researchers prospectively collect data or specimens, for a research purpose, through direct interventions or interactions with subjects or when a researcher obtains individually identifiable information for research. This includes obtaining coded data or specimens (with or without the code) that were collected by a collaborator for the same research purpose. For example, when research collaborators at another site obtain specimens through intervention with a human subject, the NIH researchers are also engaged in human subjects research when working on the same research purpose (even if the specimens are coded). (In other circumstances as described in Section 5.7 and SOP 6, IRB review of NIH activities may not always be required.)

5.6 IRB Review of Secondary Use of Identifiable Human Data or Specimens

A. When researchers propose a new research study using previously collected specimens and/or data collected for a purpose other than the currently proposed research (e.g., it is a secondary use) and can identify the subjects who provided the

[4] See the OHRP Guidance on Engagement of Institutions in Human Subjects Research and the Human Subjects Regulations Decision Charts.

specimens or data (that is, have access to individually identifiable information either directly or through coded information with a key to the code), a researcher must submit a written request (i.e., an amendment or new protocol) to an IRB that includes the following:

1. The nature of the proposed research with a complete description of the samples or data;

2. A justification for use of the identities or codes of the sources of samples or data, and, in the case of codes, a description of the ease or difficulty with which linkage can be made between the code and the source, and a description of who can make the linkage;

3. A description of the extent to which confidentiality of research data will be maintained;

4. The informed consent document which allows this use of the specimens and data, or a request for IRB waiver of informed consent (See Section B.).

5. The protocol must state how the samples, specimens and/or data will be stored, how they will be tracked, and what circumstances would prompt the PI to report to the IRB loss or destruction of samples.

B. When research involves stored samples or data with identifiers previously collected, and/or for a purpose other than the currently proposed research, an important question is whether the NIH consent signed in the initial collection protocol is sufficient for the proposed research activity. The IRB should pay special attention to requests for waiver of informed consent. To waive informed consent for research, Federal regulations currently require that an IRB document in its minutes that the following four conditions have been met:

1. The research involves no more than minimal risk;

2. The waiver will not adversely affect the rights and welfare of the subjects

3. The research could not practicably be carried out without the waiver; and

4. Whenever appropriate, the subjects will be provided with the additional pertinent information derived from the new study.

Additionally, in those cases where a waiver of informed consent is sought, the protocol should contain a statement that the subject(s) who provided the specimens or data will not be contacted by anyone connected with the research without prior approval by the IRB.

If an NIH investigator(s) wishes to conduct a research collaboration in which he/she has identifiable specimens and data, but wants to send data or specimens that are either coded or otherwise not individually identifiable to collaborators outside NIH, the NIH investigator must obtain IRB approval of an amendment to the original protocol or IRB approval of a new protocol. See 5.5.F for information regarding collaboration and transfer agreements.

5.9 Points to Consider When a Repository Is Created at NIH

An NIH IRB must approve and maintain oversight of specimen repositories that contain identifiable data or specimens (including coded information with a key to the code).

A. OHSRP must approve the creation and distribution of data and/or specimen repositories that do not contain identifiable data.

B. When creating repositories, NIH researchers should consider the following issues:

1. How were data and specimens initially collected, i.e. clinical testing or research? If research, was the collection consistent with 45 CFR 46?

2. Is there a link (a “code”) to the subjects who are the source of the data or the specimens? If so, who retains the key to the code linking data to subjects?

3. Does the repository have standard operating procedures pertaining to collection of data/specimens, removal of data/specimens, access to information and distribution of specimens and/or data?

4. What protections exist to protect the confidentiality of the research subjects (i.e. what is the system for removing identifiable information)?

5. Could the research activity lead to possible identification of research subjects?

6. If data about subject identifiers are retained, do subjects have the opportunity to withdraw consent for the use of their identifiable specimens and/or data?

7. Is there a benefit for community or expert consultation for establishing repositories with samples from specific populations or groups? For example, does the local context need to be considered (See SOP 20B).

8. Does the repository have a data use agreement (DUA) or Human Material Transfer Agreement (hMTA) for deposit or removal of specimens/data from the repository? Typically, these agreements focus on ensuring that: future researchers will not try to identify the subjects; the specimens will only be used for the approved research; if the specimens are coded, the code will not be shared with the receiving party; specimens or data will not be further distributed; notification and possible review will occur prior to publication. Also worth consideration is whether there will be future deposits (additions) to the repository by other researchers either from NIH or other institutions. There should be a standard DUA or hMTA for deposits or withdrawal of such data or specimens. For guidance on such agreements, contact your IC's Technology Development Coordinator

9. Does the repository have a system for tracking specimens/data? What is the preference for disposition of the material at the end of a research project?

10. If the collection or release of specimens and/or data involves researchers or materials originating from protocols or repositories in another country), are the SOPs of the NIH repository consistent with the HHS Human Subjects regulations (45 CFR 46)?

11. Do any other federal policies apply to repository research activities, such as the NIH policy for Genome-Wide Association Studies (GWAS)?

12. Is there a need for a standard transfer agreement for receiving specimens from another repository or researcher? May non-NIH researchers deposit and, if so, is there a standard deposit form? Contact an IC Technology Development Coordinator for guidance.

13. Has a NIH Privacy Act Officer performed a privacy impact assessment of the repository to determine what safety measures and policies apply to NIH storage and distribution of the specimens/data?

CHAPTER 6: COLLABORATIVE RESEARCH AND AGREEMENTS

SOP 20A – Obtaining a Reliance (Authorization) Agreement at the NIH
Version 3, 5-13-2016

20A.2 Policy

NIH complies with 45 CFR 46.114 and, when applicable, 21 CFR 56.114. This Standard Operating Procedure (SOP) contains the NIH policy requirements for obtaining Reliance Agreements.

20A.9 Additional Requirements for a Reliance (Authorization) Agreement When an Outside Institution Relies on an NIH IRB

Consent forms: If NIH is the IRB of Record, the NIH IRB must review the consent forms to be used at the study sites including any local required template language, (see SOP 12).

20A.11 IRB Responsibilities when There Is a Reliance (Authorization) Agreement

As set forth in a reliance agreement, the IRB of Record will conform to 45 CFR 46, FDA regulations, when applicable, and the institution's written human research protections policies and standard operating procedures, including:

A. Perform initial full board review and approval (or disapproval) at convened meetings (unless expedited review is warranted);

B. Perform continuing review at appropriate intervals;

C. Review and approve study amendments;

D. Conduct review of unanticipated problems, and serious and/or continuing non-compliance;

E. Maintain an IRB membership that satisfies the requirements of 45 CFR 46 and 21 CFR 56;

F. If necessary, suspend or terminate the research;

G. Maintain appropriate protocol and IRB records, including a copy of the reliance agreement;

H. Evaluate “local context” issues, including state, local or institutional requirements related to the protection of human subjects (see 20B - NIH IRB Responsibilities When Reviewing Local Context Considerations for Offsite Research);

I. If an NIH IRB, the IRB will notify OHSRP of any changes to or termination of the reliance agreement;

J. Abide by the terms of the reliance agreement;

K. Ensure that the correct expertise is present when a protocol is reviewed;

L. Comply with institutional policies for IRB review;

M. Inform researchers at a relying institution of all changes to the protocol[5];

N. Comply with OHRP and FDA requirements, if applicable, for IRB registration.

SOP 20B – NIH IRB Responsibilities When Reviewing Local Context Considerations for Offsite Research
Version 4, 5-26-2016

20B.2 Policy

NIH complies with OHRP (45 CFR 46) and, when applicable, FDA (21 CFR 56) requirements for approving and overseeing human subjects research that involves NIH investigators conducting research at other sites or when other institutions rely upon an NIH IRB. When an NIH IRB reviews human subjects research conducted at non-NIH sites, the NIH IRB should ensure that it possesses sufficient knowledge of the local research context to satisfy the requirements of 45 CFR 46.111, i.e., that subject selection is equitable; subjects’ privacy and confidentiality is protected; informed consent is sought in language understandable to the subject and under conditions that minimize the possibility of coercion or undue influence; and that appropriate safeguards are in place to protect the rights and welfare of vulnerable subjects. Local context review is applicable when there is an agreement to rely on an NIH IRB by a non-NIH institution and when there is dual IRB review. Consideration of local context must be documented in the deliberations of the NIH IRB when reviewing and approving research conducted at non-NIH institutions (see **Sections 20B.4 and 20B.5** below).

[5] IRB and institutional responsibilities are set forth in the reliance agreement itself. However, if a non-NIH investigator is relying on an NIH IRB as an AI on an NIH protocol, the NIH PI must communicate to the AI any information that is required communication for all AI’s.

20B.4 General Considerations for Review of Research Conducted at Non-NIH Sites

Local context should be considered when there is an agreement to rely on an NIH IRB by a non-NIH institution or when there is dual IRB review. In order to make certain that local context issues are properly considered, NIH may choose to have dual IRB review, e.g., by a joint IRB agreement (see SOP 20).

An IRB also should evaluate whether researchers at the non-NIH site are engaged in human subjects research for the particular protocol. If engaged, those researchers must be part of an FWA holding institution, or have the NIH FWA extended to cover their research activities unless, for foreign sites, OHRP determines that the procedures prescribed by the non-NIH institution afford protections that are at least equivalent to those provided in 45 CFR 46. OHRP may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy (45 CFR 46) however, thus far, OHRP has not determined that such protections are at least equivalent to 45 CFR 46.

Additionally, those researchers must have IRB approval through either an IRB affiliated with their FWA or through a reliance agreement between the NIH and their institution, to rely on the NIH IRB. Unless the study has a coordinating center responsible for validating that FWA's for all sites remain current, the NIH IRB should confirm that the PI has completed the section of the continuing review application confirming that the relying sites have an active FWA.

20B.5 Local Context Considerations

IRBs must be mindful of the communities in which research will be carried out. Community issues may vary and IRBs should consider the following factors, as applicable:

A. **State and local laws:** IRBs should be aware and mindful that Federal law, i.e., 45 CFR 46, may, in some instances, diverge from state and local law. While 45 CFR 46 must be met for research to be approved, varying state and/or local requirements that are not inconsistent with 45 CFR 46 need not be considered problematic. In the event of real or apparent conflict, the IRB may consult the NIH Office of the General Counsel for further assistance.

B. Local attitude(s) towards medical research or research in general;

C. Language barriers, illiteracy or lack of a written language;

D. Variability in the age of majority;

E. Research subjects' potential cultural differences/sensitivities, such as stigma associated with the health issue under study, gender roles or privacy issues (e.g. modesty concerns during protocol procedures);

F. A study site that differs significantly from other sites because of variable ethnicity or national origin, religion or customs;

G. If the research activities involve greater than minimal risk to subjects and investigators at the outside site are interacting with subjects, the NIH IRB must document the manner in which it has obtained appropriate information about the local research context. Possible options for doing this include, but are not limited to:

1. One or more of the IRB members has knowledge of the local research context gained through direct experience with the non-local research site, the subject populations, and the local community;

2. A knowledgeable consultant participates in the IRB Committee discussion of the study or provides a prior written review and is available during the IRB meeting;

3. An experienced PI with a history working with the local population/community.

IRBs may choose to use the Local Research Context Forms (**Appendix B-Initial Review Local Context Worksheet and Appendix C-Continuing Review Local Context Worksheet** in SOP 20B) for obtaining local context information from other sites.

20B.6 NIH IRB Review of Human Subjects Research Conducted at International Sites

When an NIH Investigator is planning to conduct research in a foreign country, the IRB should take into consideration the following issues:

A. **Local Conditions:** The PI should provide information about the culture, economic and political conditions, and specify any risks to subjects specific to that site that may impact research.[6] The IRB may use consultants familiar with the population to

1. While not an IRB responsibility, the PI should consider travel/business restrictions when the performance site is in a foreign country. There should be no U.S. Government restrictions about conducting research in that country. Additional information about such restrictions is available at the Division of International Relations at Fogarty International Center (see References below.)

aid in their deliberations. Consultants should include individuals with knowledge of the local research context (see also **20B.5 G** above).

B. **Dual Review:** In addition to the NIH IRB review, the research may also be subject to approval of a local IRB or Ethics Committee (EC). IRB/EC approval may be obtained from an institution/entity associated with that country that has a current approved FWA and an IRB/EC registered with OHRP. Some countries require approval from the Ministry of Health or other government entities or officials. For more information, contact the Division of International Relations at Fogarty International Center (FIC) (see **References** in SOP 20B for the link to the OHRP website to search for foreign institutions holding FWAs and IRB registrations; for the OHRP International Compilation of Human Research Standards, and for the FIC contact information.) Additionally, the NIAID website, *ClinRegs*, provides an on-line database of country- specific clinical research regulatory information. (See **References** in SOP 20B for this link.)

C. The NIH usually requires that the NIH IRB review and approve the protocol before it is submitted to the in-country IRB/EC.

IRBs should refer to Appendix A-Points to Consider When Reviewing International Research in SOP 20B for more considerations.

20B.7 Examples of Methods by Which an NIH IRB Can Evaluate Local Context

When an NIH IRB is engaged in collaborative research involving enrollment of subjects or data collection at non-NIH sites, the issue of local context must be addressed and documented by the IRB, using one or more of these methods:

- Non-NIH IRB review at the local site and feedback to the NIH IRB
- Information provided by the local lead investigator at a non-NIH site
- Completion of the NIH local context form by lead investigator non-NIH site (See **Initial Review Local Context Worksheet and Continuing Review Local Context Worksheet in Appendices B and C**, respectively.)
- Expertise of an NIH IRB member or an ad-hoc IRB consultant
- Long-standing or prior NIH IRB experience with the non-NIH site (i.e. NIH IRB expertise about that site)

20B.8 NIH IRB Review of Research Conducted at Native American Reservations or at an Entity that Focuses on Native American Populations

A. When the performance site is located on a Native American reservation or an entity that focuses on Native American populations, an IRB should consider information about the culture, economic and political conditions, and risks specific to that site and applicable laws. Consultants familiar with the population may aid in these deliberations. Consultants could include individuals with personal knowledge of the local research context, such knowledge having been obtained through extended experience with the research institution, its subject populations and/or its surrounding communities.

B. All human subjects research conducted in Indian Health Service (IHS) facilities, in Tribally managed, Urban facilities (sites for Urban Indian Health Programs) or with IHS staff or resources must be approved by an IHS IRB (all of which fall under the IHS federal-wide assurance FWA00008894). The *sole* exception to this is that urban or Tribally managed facilities may obtain their own independent FWA with OHRP. In that case, the Tribe may use an IHS IRB or any other IRB of its own choosing. The IHS encourages (and will assist) Tribally-managed health programs engaging in research to obtain independent FWAs. (See **References** in SOP 20B for the link to the IHS Research Program.)

C. Research projects at IHS direct care facilities serving a Tribal Nation that has its own IRB must have the approval of *both* the Tribal IRB *and* the IHS IRB. Projects at facilities managed by the Tribal Nations with their own IRB and FWA require approval of *only* the Tribal IRB.

D. IHS approved research conducted in facilities serving specific Tribes must first obtain formal, written approval of the appropriate Tribal government(s). This approval must be submitted with the original application to the IHS IRB.

SOP 20C – Responsibilities When the NIH Intramural Research Program Serves as a Coordinating Center for a Multi-Site Trial
Version 2, 3-2-2016

20C.2 Policy

When the NIH Intramural Research Program is responsible for leading a Coordinating Center for multisite human subjects research or when an NIH IRB is the IRB of record for a non-NIH Coordinating Center, the NIH IRB will review the study protocol, consent form templates (unless these activities are being performed by a Central IRB) and protocol application outlining Coordinating Center responsibilities for collection, storage,

management, and (if applicable) analysis of data collected on subjects from all sites involved in a multisite trial. The NIH IRB review will determine and document that the Coordinating Center has sufficient mechanisms in place to ensure (i) adherence to 45 CFR 46 at all sites; (ii) that the privacy of subjects and the confidentiality of data are adequately maintained; and (iii) that the protocol(s) is reviewed and approved by an IRB for the collaborating institution(s) engaged in human subjects research prior to transmission of data. Additionally, the NIH IRB will confirm that there is a reliance agreement between the non-NIH Coordinating Center and NIH.

20C.7 IRB Responsibilities when Reviewing Protocols for which the NIH Will Serve as the Coordinating Center

If the NIH Intramural Research Program serves as a Coordinating Center for a multisite trial, an NIH IRB should review the Coordinating Center's protocol (which may be part of the larger study protocol if NIH will also be a study performance site) and its standard operating procedures. The purpose of the review is to determine whether the Coordinating Center has sufficient mechanisms in place to ensure that, where applicable:

A. Sample protocol and informed consent documents are developed and distributed to each collaborating institution;

B. Unless a Central IRB will be utilized, a process is in place for each site to submit the sample protocol and consent from templates to their IRB;

C. There is a plan for central maintenance of site IRB reviews and approvals;

D. There is a plan for how data will be sent to the data coordinating center and how subject confidentiality and related data will be protected;

E. There are adequate data management, data analysis, and data safety monitoring plans, given the nature of the research;

F. Each collaborating institution holds an approved FWA;

G. Each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects, or there is a signed authorization agreement for the site to rely on the IRB of another entity;

H. Any substantive modification by the collaborating institution of sample consent information related to risks or alternative procedures is appropriately justified;

I. Informed consent is obtained from each subject in compliance with HHS regulations;

J. Start-up meetings and any site training sessions required prior to subject enrollment are described;

K. There is a process and monitoring plan for provision/distribution of study related drugs or devices, if the Coordinating Center will be responsible;

L. There is a plan in place for study site monitoring and study progress and/or protocol compliance monitoring, if the Coordinating Center will be responsible.

20C.8 IRB Responsibilities when Reviewing Protocols for which a Non-NIH Site Will Serve as the Coordinating Center

In addition to the requirements noted above, when an NIH IRB is serving as a Central IRB for a multisite study, it may also be the IRB of record for the non-NIH Coordinating Center. Often Coordinating Centers do not have direct interaction with subjects and, instead, perform administrative functions. The IRB should be aware that the principal risk in such cases is possible breach of confidentiality. While responsibilities of Coordinating Centers may vary as noted in Section 20.C.7, the IRB must determine whether the Coordinating Center has sufficient mechanisms in place to ensure that the data analysis, and data safety and monitoring plans are adequate. If the Coordinating Center will be performing data management or statistical analyses, the IRB should review and document that there is an adequate plan to protect both subject privacy as well as confidentiality of the data. If the Coordinating Center or statistical analysis center will have access to identifiable data, the IRB should confirm that the entity has an FWA.

Additionally, the NIH IRB must notify OHSRP who will promptly inform the Coordinating Center of any IRB determinations resulting in protocol suspension of either study enrollment, study intervention, or approval of the entire study at any/all sites as well as termination at any/all of the sites for which it is serving as the IRB of record. The NIH IRB must also notify OHSRP who will notify the Coordinating Center of any IRB determination of trial-wide unanticipated problems or noncompliance affecting the research at any/all of the study sites.

CHAPTER 7: ADDITIONAL IRB RESPONSIBILITIES

SOP 25 – Training Requirements for the NIH Human Research Protection Program (HRPP)
Version 3, 2-11-2014

25.2 Policy

All Intramural Research Program (IRP) scientists are required to complete training in order to assure that they understand when research activities involve human subjects research and what is required when they conduct this type of research.

Clinical researchers and clinical research support staff are required to have additional training commensurate with their roles and responsibilities. This includes Good Clinical Practice (GCP) training when research is regulated by the Food and Drug Administration (FDA) (see SOP 15). IRBs may require additional training for investigators who do not demonstrate understanding of specific areas or when investigators undertake a new type of research (for example, research with prisoners).

25.5 Training Requirements for the NIH HRPP Community

25.5.4 HRPP Staff: Chairs, Members and Staff of the NIH IRBs and OHSRP Professional Staff

Courses are accessed via the HRPP Training page (see Appendix 2, item J in SOP 25). Non-NIH IRB members should contact OHSRP to gain access to the required training resources.

A. All HRPP Staff including IRB Chairs and Members, IRB Administrative Staff, and OHSRP professional staff

1. Required training:

    a. NIH Clinical Research Training (CRT); or

    b. CITI Biomedical course or CITI Social and Behavioral course; or

    c. The Ethical and Regulatory Aspects of Clinical Research offered by CC Bioethics.

2. Either the NIAID GCP course or the CITI GCP for PI's course

3. **Optional or Just-in-time Training:** The IRB Chair may determine that the additional CITI modules will be required according to the type of research reviewed by the IRB, but are otherwise optional, see Section 25.5.5 below.

B. Incoming IRB Members

In addition to the requirements listed above, incoming IRB members must also complete the following requirements prior to becoming an active member:

1. Required training:

    a. NIH IRB Member Training, (see Appendix 2 in SOP 25 for the link)
    b. Attend the OHSRP IRB member in-person orientation; and
    c. Attend and observe one IRB meeting in-person

25.5.5 Optional or Just-In-Time Training

In general, the just-in-time CITI courses listed below are optional (e.g. GCP courses are optional, for investigators who do not conduct FDA-regulated research.) However, IRBs or PIs may require investigators or non-investigator research staff to complete these courses and IRB Chairs may require IRB members or staff to take these courses based on the type of research reviewed by the IRB. If protocol-specific training is required by the IRB, the IRB should document the specific requirement. A stipulation is one mechanism to document a protocol-specific requirement; for more information about verifying compliance see Sections 25.7 and 25.9 below.

A. Biomedical- Vulnerable Subjects - Research with Children

B. Biomedical- Vulnerable Subjects- Research with Pregnant Women, Human Fetuses or Neonates

C. Biomedical- Vulnerable Subjects- Research with Prisoners

D. Biomedical- Vulnerable Subjects- Workers/Employees

E. Genetic Research in Human Populations

F. Stem Cell Research Oversight

G. NIAID GCP course

H. CITI GCP modules

I. International Studies- ICH Overview and ICH- Comparison Between ICH GCP E6 and US FDA Regulations, available to those staff who complete the CITI GCP course

J. Unanticipated Problems and Reporting Requirements in Biomedical Research

K. Unanticipated Problems and Reporting Requirements in Social and Behavioral Research

SOP 26 – Evaluation of NIH IRB Chairs, Vice Chairs and Members, IRB Administrative Staff and IRB Committee Activities
Version 3, 6-9-2016

26.2 Policy

NIH officials conduct periodic evaluations of IRB Chairs and Vice Chairs, IRB members, IRB activities and IRB administrative staff to assure that the NIH IRBs comply with regulatory requirements and the NIH HRPP SOPs, and to identify areas that need improvement, and to justify changes, when needed.

26.3 Procedures and Officials Responsible for Evaluation Activities

26.3.1 Evaluation of NIH IRB Chairs

A. An NIH IRB Chair will receive a written copy of performance standards for his/her activities as Chair, through the HHS Employee Performance Plan (Form HHS-704B) or through a contract, as applicable. The performance standards addressing his/her performance as IRB Chair consist of one or more critical elements, depending on whether the Chair's IRB activities are full- or part-time. This evaluation will take place consistent with the HHS performance plan or contract requirements. Appendix A in SOP 26 contains sample language for these performance standards.

B. The Director, OHSRP or designee will evaluate the performance of all NIH IRB Chairs by attending each IRB meeting at least annually or more frequently, if necessary. S/he may seek information from IRB members and others as appropriate.

C. Standards for IRB Chair evaluation are contained in **Appendix B** in SOP 26.

D. If at any time, issues related to a Chair's leadership, knowledge or performance are identified, the OHSRP Director will discuss them with the Institutional Official (IO, the Deputy Director for Intramural Research (DDIR)) and with the Chair. If appropriate, a plan for improvement may be implemented, including but not limited to, additional educational and/or mentoring activities. Failure to perform acceptably despite an improvement plan may result in being removed as IRB Chair as determined by the Institutional Official.

26.3.2 Evaluation of NIH IRB Vice Chairs

A. The Vice Chair will be evaluated annually by the IRB Chair according the elements that are applicable to the Vice Chair's responsibilities listed in **Appendix B** in SOP 26 for IRB Chairs.

B. Any issues related to the Vice-Chair's performance will be discussed and a plan for improvement may be implemented. Failure to perform acceptably despite an improvement plan may result in being removed as Vice Chair as determined by the Institutional Official.

26.4 Evaluation of NIH IRB Members

A. Primary IRB members will be evaluated at least annually to assess their knowledge of ethical principles and basic regulatory requirements, attendance at, preparedness for and participation in meetings. Alternate IRB members, who have attended a minimum of 3 meetings, will be evaluated at least annually to assess their knowledge of ethical principles and basic regulatory requirements, preparedness for and participation in meetings. See **Appendix C** for IRB member performance elements and see **Appendix F: IRB Member Evaluation Instrument** in SOP 26.

B. These evaluations are delegated by OHSRP to the IRB Chair. The IRB Chair will perform these evaluations about the members' function on the IRB based on his/her observations at convened meetings or through other appropriate means. Information about performance also may be obtained from self-evaluation activities and/or from other IRB members and the Chair.

C. Any issues related to members' performance will be discussed and a plan for improvement may be implemented. Failure to perform acceptably despite an improvement plan may result in being removed from membership on the IRB as determined by the IO.

SOP 27 – Transfer of Protocols Between Institutional Review Boards (IRBS)
Version 1, 3-7-2016

27.2 Policy

Transfer of previously approved protocols from one IRB to another should be accomplished in a way that assures continuous IRB oversight with no lapse in either IRB approval or the protection of human subjects and with minimal disruption to subjects and research activities. Office of Human Subjects Research Protections (OHSRP) is delegated to provide oversight for the protocol transfer process relating to NIH intramural IRBs.

When transferring protocols, prior approval must be sought from the NIH Investigator's IC Officials (Clinical Director (CD) or Scientific Director (SD), as appropriate, and from the Director, OHSRP who will obtain input from the NIH IRB Chair(s).

When transferring between the NIH and a non-NIH institution, a written protocol transfer agreement is required and a reliance agreement may be required. Transfers between NIH IRBs should have a written agreement. For more information for the requirements for reliance, see SOP 20A.

27.4.1 Baseline Responsibilities and Documentation

The following responsibilities are to be satisfied and appropriately documented in a written agreement when applicable:

A. **Identify those studies for which IRB oversight is being transferred:** One of the first actions in the transfer process is determining those studies for which IRB oversight is being transferred to ensure effective planning and continuity.

B. Establish an effective date for transfer of oversight for the clinical investigation(s):

    1. A transfer date for each protocol for which oversight is being transferred should be determined. Such an action promotes continuity, helps prevent a lapse in IRB coverage, and minimizes confusion regarding which IRB is responsible for review and action if, for example, an unanticipated problem should arise or research needs to be quickly suspended or terminated.

    2. The exact transfer date may be specified in advance or the date may be made contingent upon the review and acceptance of the research project by the receiving IRB. When a large number of research projects are being

transferred, it may be preferable to phase-in the transfer over a period of weeks or months to facilitate a smooth transition. If oversight is being transferred because of the closure of an IRB, the original IRB should inform all investigators and/institutions, as appropriate, of the pending closure date.

3. If there is difficulty working out effective dates for protocol transfers between IRBs, please contact OHSRP.

C. Ensure the availability and retention of pertinent records:

1. Availability of records:

a. If the original and receiving IRBs are both within the intramural research program (IRP), records regarding the research projects affected by the transfer must be transferred to the appropriate electronic system for the receiving IRB (PTMS, iRIS™ etc.).

b. If both the original and receiving IRBs are not within the IRP, before the receiving IRB accepts oversight of the transferred research project, it should obtain copies of all pertinent records.

c. The original IRB should make pertinent records available to the receiving IRB as follows:

i. Scientific Review(s)

ii. Research protocol

iii. Consent form(s)

iv. Investigator's brochure (or other relevant attachments)

v. Continuing Review (CR) memorandums or other progress reports submitted by the investigator for review by the IRB

vi. Statements of significant new findings provided to subjects

vii. Copies of all correspondence between the IRB and the investigator

viii. Any other relevant submissions to the IRB, including but not limited to amendments and reports of problems.

d. The receiving IRB should also obtain meeting minutes from the original IRB's reviews of the protocol as this information may be critical to the receiving IRB's assessment of the adequacy of the previous review (e.g., discussion of controverted issues, quorum, etc.).

e. Both the original IRB and the receiving IRB should maintain adequate records regarding the research projects affected by the transfer. Such records should include any written agreement between the original and receiving IRBs, the title of the protocols being transferred, the research sites affected, the names of the investigators, the identities of the original IRB and the receiving IRB, and the date(s) on which the receiving IRB accepts responsibility for oversight of the research projects. In addition, the original and receiving IRBs should keep records of all communications to all affected investigators. For more information about retention of IRB records, see SOP 4.

2. **Retention of IRB records:** An engaged institution must be able to access documentation of IRB activities and records relating to the research project for at least 3 years after completion of the research at the engaged institution (45 CFR 46.115(b)). In addition, the records must be accessible for inspection and copying by OHRP at reasonable times and in a reasonable manner. If the receiving IRB is an NIH IRB, IRB records relating to the protocol shall be retained for at least 3 years after completion of the research as per SOP 4. Factors to consider in selecting an appropriate record retention arrangement may include the reasons for the transfer, as well as the nature of the research projects and the records.

27.4.2 Additional Responsibilities and Documentation

The following responsibilities should be considered. If applicable, the responsibilities should be implemented and appropriately captured in the written agreement between the parties.

A. Conduct a review of the study(ies) by the receiving IRB, where appropriate, before it accepts responsibility for the study(ies):

1. Continuing Review of research when transferring between NIH IRBs:

a. When the research project is transferred from one NIH IRB to another NIH IRB or the research project remains at the same engaged institution, the receiving IRB is not required to review the project prior to the next CR date established by the original IRB, however such a review may be done depending on the circumstances of the transfer and characteristics of the specific research project. The receiving IRB may decide to undertake an initial review (IR) or a CR (either by the convened IRB or under an expedited review procedure, if appropriate).

b. Alternatively, the receiving IRB may decide not to conduct any review prior to the next continuing review date established by the original IRB; especially if such a review is not deemed to substantively add to human subject protections. In such a circumstance, some receiving IRBs nonetheless may request that the IRB chairperson, another IRB member, an IRB administrator, or another qualified administrative staff member perform an informal assessment of the research project.

2. **Initial or Continuing Review of research by the receiving NIH IRB when being transferred from a non-NIH IRB:** When the research project moves to the NIH and responsibility for review is transferred to an NIH IRB, the receiving IRB must conduct an IR or CR of the research project before the NIH becomes engaged in the human subjects research project (45 CFR 46.103(b)) unless there is a reliance agreement in place for the NIH to rely on the original IRB at the original institution in which case a new IR or CR is not necessary. It may be appropriate for a protocol amendment to be submitted to the original IRB to notify them of the change in location of the research.

3. **Initial or Continuing Review of research by the receiving non-NIH IRB when being transferred from an NIH IRB:** When the NIH research project moves to a new institution and responsibility for review is transferred to another IRB, the non-NIH IRB is expected to conduct an IR or CR of the research project before the new institution becomes engaged in the human subjects research project (45 CFR 46.103(b)). In such a case, a protocol amendment must be submitted to the NIH IRB to notify them of the change in location of the research. This amendment may constitute a minor change to the research, in which case the NIH IRB may choose to use expedited procedures to review.

4. **Suspension or Termination:** Receiving IRBs have the authority to suspend or terminate approval of research under certain circumstances, for example, when the research project is not being conducted in accordance with the receiving IRB's requirements or has been associated with unexpected serious harm to subjects (45 CFR 46.113). IRBs should ensure that the rights and welfare of currently enrolled subjects are protected, subjects are not put at risk, and subjects receive appropriate care during any period in which the IRB and clinical investigator are attempting to resolve any issues. The receiving IRB must also promptly report, including the reasons for the suspension or termination, to the investigator, institutional officials and, if at NIH, also to OHSRP who will subsequently report the suspension or termination of IRB approval to OHRP (45 CFR 46.103(b)(5)).

B. Confirm or establish the date for the next continuing review:

1. If the receiving NIH IRB performs a review at the time of research project transfer (whether an IR or a CR), it may to choose to maintain the anniversary date established by the original IRB or establish a new date of approval. If it is decided that a new anniversary date will be established, the new date must be within one year of the receiving NIH IRB's approval. For more information about establishing and maintaining anniversary dates, see SOP 9.

2. If the receiving NIH IRB does not conduct an IR or CR at the time of transfer, the date of research project approval by the original IRB is presumed to remain in effect for the full approval period established at the time of the most recent review by the original IRB.

3. In the unforeseen circumstance that the protocol is transitioning close to its expiration date, in order to avoid a lapse in IRB review, if the receiving IRB is unable to complete the CR prior to the current expiration date of the protocol, the original IRB should provide the review and the effective date of the transfer should be updated accordingly.

C. Determine whether the consent form needs to be revised:

1. Under 45 CFR 46.116(a)(7), the informed consent document is required to contain "[a]n explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject". Therefore, if a change in IRB oversight results in changes in the contact information

regarding subject rights and/or whom to contact in the event of research-related injury, the new contact information must be provided promptly to subjects (45 CFR 46.116(a)(7)). For subjects who were previously enrolled, this may be accomplished in a number of ways, for example, with a letter providing the relevant contact information. For new subjects, the informed consent, assent, and/or parental permission form must be revised to reflect the new contact information (45 CFR 46.116(a)(7)).

2. Other changes to the consent form may also be necessary if the receiving NIH IRB requires modifications to the consent form at the site(s) under its jurisdiction as a condition of approval (e.g., changes in template language, changes in risks, etc.) (45 CFR 46.109(a) and (b)). The required changes may be conveyed to the investigator as stipulations to secure IRB approval for the research at that site or sites (see, e.g., 45 CFR 46.109(a)).

D. Notify the key parties (e.g., investigator, Data Safety Monitoring Board, Office of Protocol Services (OPS), etc.) of the transfer of responsibility of IRB review as soon as possible, and provide contact information of the receiving IRB.

E. **Address IRB regulatory issues:** If an NIH IRB is the receiving IRB, the processes for reviews and actions should be consistent with the NIH HRPP SOPs. Problem reports submitted for potential unanticipated problems, protocol deviations or noncompliance should be reviewed by the appropriate IRB (original vs. receiving IRB) based on the effective date of the transfer. As such, IRB review of potential unanticipated problems, deviations and noncompliance should follow applicable NIH HRPP polices (see SOP 16 and SOP 16A).

F. **Central IRBs:** For studies for which the original IRB acts as a central IRB, those local institutions/IRBs that have written agreements to rely on the original IRB for review responsibility should be notified that responsibility for the study is now being transferred to a new central IRB (receiving IRB). Local institutions/IRBs should be given the option to enter into new written agreements with the receiving IRB or opt out of the central review arrangement if they do not believe central review by the receiving IRB is appropriate for their local institution.

G. **Temporary Transfers:** Sometimes the transfer to a receiving IRB is temporary and the responsibility for IRB review eventually will revert back to the original IRB. This may be the case when a natural disaster temporarily disrupts the functioning of an IRB. In such instances, the transfer procedure back to the original IRB may only involve:

1. Identifying studies for which IRB oversight is being transferred;

2. Ensuring availability and retention of pertinent records;

3. Establishing an effective date for transfer of oversight; and

4. Notifying the key parties.

Appropriate actions depend on the specific circumstances of the transfer.

27.4.3 Process for Transfer of Protocols that are also FDA Regulated

Further considerations for FDA-regulated research in addition to the above:
Entities involved in a transfer of IRB review responsibilities for a clinical investigation include not only the original IRB and the receiving IRB but also involve the sponsor who initiates the clinical investigation and the clinical investigator who conducts the investigation. The investigator may also be the study sponsor (sponsor investigator) (see SOPs 15, 15A and 15B).

The process for transfer of protocols regulated by the FDA is very similar to the steps listed above (see FDA: Guidance for IRBs, Clinical Investigators and Sponsors Considerations When Transferring Clinical Investigation Oversight to Another IRB in **References** in SOP 27). Additional requirements and concerns regarding FDA regulated clinical investigations include the following:

A. Ensure the availability and retention of pertinent records:

1. **Access:** Since FDA may require access to the records at any reasonable time, it is important for the parties to agree which entity (e.g., the original IRB, the receiving IRB, the institution that housed the original IRB, a Contract Research Organization (CRO) or other responsible third party) will maintain the records once clinical investigation oversight has been transferred. Whichever party assumes responsibility for the records is responsible for ensuring that they are retained in accordance with 21 CFR 56.115(b).

2. **Availability of pertinent records:** In addition, the original and receiving IRBs should keep adequate records of all communications to all affected sponsors, clinical investigators, and FDA, and comply with all other recordkeeping requirements

3. **Retention of records:** There may be circumstances where the original IRB reaches an agreement with the receiving IRB to retain some of the documentation for the transferred trials, yet may not be able to commit to retaining the documents for at least 3 years after the completion of the research (21 CFR 56.115(b)). This situation may arise, for example, where an IRB ceases operations yet retains responsibility for some records for trials that are still ongoing, either by physically maintaining these records or by reaching a storage arrangement with a responsible third party. In this instance, the original IRB should contact the FDA to discuss possible retention arrangements.

B. **Notifying key parties:** After IRB transfer of oversight for the clinical investigation is complete, the sponsor must update the associated IND or IDE with the name and contact information of the receiving IRB, and should include the effective date of transfer.

C. **Suspensions and terminations:** The NIH sponsor reporting policy/ies should be considered and addressed as applicable (see SOP 15). For example, if an NIH IRB terminates or suspends its approval of a trial, the PI will inform the sponsor, and OHSRP will report the suspension or termination of IRB approval to FDA (21 CFR 56.108(b)) (see SOP 11 and SOP 24).

D. **Contacting FDA:** An original or receiving IRB may have questions that are not resolvable through communications with the sponsor or clinical investigator. In such situations, either IRB may contact FDA for additional guidance. Affected sponsors and clinical investigators may also contact FDA in these situations.

27.5 Additional Considerations

A. The protocol transfer should strive to establish mutually agreed upon and realistic timelines for transfer which assures continuous IRB oversight with no lapse in IRB approval or the protection of human subjects and which will result in minimal, if any, disruption of research activities.

B. At NIH, plans for protocol transfers should include the various NIH stakeholders, such as the study PI, Clinical Director (CD), Scientific Director (SD), OHSRP, sponsor and OGC, as appropriate.

C. A comprehensive checklist of items to be included in the protocol record may be provided to the original non-NIH IRB that will transfer the protocol to a receiving NIH IRB.

D. **IRB composition:** The receiving NIH IRB should have members with sufficient background to promote complete and adequate review of research activities associated with the protocol being transferred (e.g. for research regulated by the FDA, the Board must be able to apply FDA regulations in its review). For more information about NIH requirements for composition of its IRB, see SOP 2 and SOP 15.

E. Consideration needs to be given to database compatibility between systems used by the original and receiving IRBs.

F. When the receiving IRB is an NIH IRB:

1. The NIH IRB may consider auditing the study records of the original IRB, and concerns outlined in the audit report should be addressed prior to protocol transfer.

2. Applicable study records (as noted in **27.4.1.C**) covering at least the prior 3 years should be transferred (preferably electronically) to the receiving NIH IRB.

3. The NIH IRB should ensure that there will be an appropriate data and safety monitoring plan in place and such information may be included in the protocol and described in the transfer agreement, if appropriate.

4. **Scientific Review:** If the NIH IRB is receiving a protocol from a non-NIH IRB and the outside protocol is funded by an NIH grant, there is no need to address scientific review. Otherwise, the IRB will forward information to the CD about what scientific review, if any, occurred, and the CD will decide if it is adequate.

SOP 23 – Quality Management System for the NIH HRPP
Version 3, 1-14-2016

23.2 Policy

The DDIR, NIH Quality Officer, Institutes and Centers (ICs), Office of Human Subjects Research Protections (OHSRP), investigators and the IRBs work to carry out the NIH HRPP. These activities are divided among the entities (as described in **23.5**) and include the following:

A. Establish and implement NIH-wide assessment of compliance with federal regulations (45 CFR 46 and, as applicable, 21 CFR parts 50, 56, 312 and 812, see **References** in SOP 23) and NIH policies, and the quality, effectiveness and efficiency of HRPP activities;

B. Establish Quality Improvement (QI) efforts to address deficiencies in compliance and to improve the quality, effectiveness and efficiency of HRPP activities;

C. Evaluate effectiveness of IC QI efforts;

D. Ensure ongoing monitoring of individual research protocols within ICs;

E. Educate NIH personnel about Federal regulations (45 CFR 46 and, as applicable, 21 CFR parts 50, 56, 312 and 812, and **References** in SOP 23) and guidance and NIH policies that ensure protection of human research subjects;

F. Continuously review regulatory developments and guidance and incorporate these as appropriate into the HRPP;

G. Develop policies to support the HRPP.

23.4 QC/QA/QI Interactions

~~A.~~ QC, QA and QI activities intersect with other HRPP activities, particularly IRB activities. As permitted by law and policy, information should be exchanged between components of the HRPP. For example, if results of QC or QA activities indicate an unanticipated problem such as non-compliance with regulations, protocol requirements or NIH HRPP policies, this information must be reported to the relevant IRB as required by SOP 16 and SOP 16A.

B. Compliance problems that are identified during the course of quality assurance activities should be addressed following the processes outlined in SOP 16A.

23.5 Roles and Responsibilities

23.5.5 Responsibilities of the IRBS

A. Ensure that auditing and monitoring plans and potential conflict of interest are addressed in each protocol.

B. Review allegations of non-compliance as set forth in SOP 16A.

23.5.7 Shared Responsibilities

A. The IRBs, Institutes/Centers and/or OHSRP develop corrective plans as needed in response to findings of internal and external investigations and inspections.

B. The Institutes/Centers and OHSRP share responsibility for ensuring appropriate education and training of clinical investigators on their roles and responsibilities.

C. OHSRP and HSRAC determine and annually review requirements for minimal training and for refresher training for research staff.

D. OHSRP and Institutes/Centers implement corrective plans to address performance gaps.

E. OHSRP, IRBs or an institutional official receive, investigate and respond to allegations of non-compliance (see SOP 16A).

CHAPTER 8: IRB STAFF RESPONSIBILITIES

SOP 2 – IRB Membership and Structure

Version, 2-24-2016

2.2 Policy

The NIH Human Research Protection Program (HRPP) ensures that its IRBs are constituted consistent with federal regulatory requirements. It has procedures in place for (1) appointing and reappointing members; (2) maintaining current IRB rosters; (3) communicating members' responsibilities to them; (4) removing members for cause, and (5) clarifying their legal liability.

2.4 Rosters of IRB Members

2.4.1 Maintenance of Roster

Each NIH IRB must maintain a current roster (see Appendix H in SOP 2) of its membership, using the Excel template provided by OHSRP, which includes at least the following information:

A. First and Last Name

B. Earned Degrees

C. Scientific Status (scientist or non-scientist; see 2.3 above)

D. Representative Capacity (indicate which, if any, vulnerable populations are being represented by this member, e.g. children, pregnant women, or prisoners, etc.; or if the member represents the perspective of research participants)

E. Area of Specialty

F. Indications of Experience (e.g. brief description of all relevant experiences that describe each member's expected contributions to the IRB)

G. Relationship to the organization (for example, current employee, former employee, trainee, special volunteer)

H. Affiliation Status

I. IRB Role (e.g., Chair, Vice Chair, primary member or alternate member)

J. Alternates for whom (e.g. alternate for pharmacist member, etc.)

K. Phone number

L. Email address

M. Postal address

N. Term effective date

O. Appointment term

P. Gender

Q. Race/ethnicity

R. Title

S. Term End Date

T. OHSRP approval date

2.4.2 Reporting Membership Changes to OHSRP

IRB administrative staff will record changes in the IRB roster as they occur and will ensure that OHSRP has an up-to-date roster and contact information in electronic form, using the roster template provided by OHSRP. The information should include the Statement of Status as an Unaffiliated IRB Member (Appendix A in SOP 2).

Annually all members will be surveyed by their designated IRB using the IRB Member Survey template. Members will have the opportunity to update their representative capacity, affiliation, and be reminded of the need to report any undue influence[7] to OHSRP. IRBs will be notified of when to issue the survey by OHSRP. Surveys will be returned to the designated IRB and stored on SharePoint. IRBs must notify OHSRP as soon as possible whenever the affiliation or scientific designation of a member has changed.

2.4.3 Reporting Membership Changes to OHRP

OHSRP reviews IRB rosters, maintained by the IRBs, and provides membership updates to the OHRP (see the Introduction to the NIH Human Research Protection Program (HRPP)).

2.5 Appointment and Reappointment Procedures and Terms of Service

2.5.1 Procedures for Initial Appointment to the IRB

A. Identifying members: The Institute CD or CDs (in the case of multi-Institute IRBs), the IRB Chair, and, at the discretion of each IC, the SD, recommend the appointment of the IRB Chair, the IRB Vice Chair and IRB members (including alternate members). In making such recommendations, consideration will be given to the requirements above for IRB membership and representation. The designated IRB will provide the prospective nominee with the IRB Member Survey to ensure that they satisfy the IRB's composition and representative capacity requirements.

    1. Nominees and their supervisors should agree to the nomination.

[7] Undue influence means attempting to interfere with the normal functioning and decision-making of the IRB or to influence an IRB member or staff, a PI or any other member of the research team outside of established processes or normal and accepted methods, in order to obtain a particular result, decision or action by the IRB or one of its members or staff.

2. The Director, SD and CD of any IC may not serve as a member, IRB Chair or Vice Chair of any NIH IRB.

B. Nomination memorandums:

1. The designated IRB office prepares a nomination memorandum (see Appendix B in SOP 2) for the approval of the CD(s), and SD as applicable.

2. Once signed, the designated IRB should notify OHSRP by email requesting a review of the new nomination located in SharePoint.

3. OHSRP will review this information to confirm that the nominee fulfills the requirements for IRB membership and representation. OHSRP will provide the approval date in the Roster spreadsheet or notify the IRB office via email if there is a concern.
4. The designated IRB should not instruct nominees to commence training until OHSRP confirms its position.

5. Once approved by OHSRP, the signed nomination memorandum is retained by the designated IRB and a copy should be included in the appointment packet when it is forwarded to the Deputy Director for Intramural Research (DDIR) for approval.

6. The memorandum describes how the qualifications of the nominee will serve the IRB (see Appendix B in SOP 2). It specifies an appointment term (see 2.5.1.E below) and includes the following attachments:

a. *Curriculum Vitae* for the person being nominated.

b. A “Statement of Status as Unaffiliated Member of an NIH IRB” (see Appendix A in SOP 2), signed by the nominee, as applicable.

c. IRB Member Survey

C. Specific considerations for nomination of Chair and Vice Chairs: Nominees for IRB Chair and Vice Chair should have experience in human subjects research, which could include previous experience serving on an IRB; be knowledgeable about the scientific mission and clinical program of the particular Institute or Institutes for which the IRB serves as the primary IRB, and be familiar with the federal regulations for

the protection of human subjects (45 CFR 46 and 21 CFR 50 and 56) and the ethical basis for the regulations (The Belmont Report).

D. Completion of required training: Before beginning service as a member of the IRB, all nominees, including those for Chair and Vice Chair, must complete the training requirements that are specified in SOP 25 - Training Requirements for the NIH HRPP. Designated IRBs should notify nominees of their training requirements and ensure that all training requirements are met. IRBs are reminded to monitor continued compliance with training requirements for all IRB members.

E. Appointment letters: After completion of required training, the designated IRB prepares an appointment letter for approval by the DDIR. Upon approval, the designated IRB sends the approved letter to the nominee confirming their appointment to the Institute's IRB for an initial one-, two-, or three-year term (see Appendix C in SOP 2). Appointment letters are copied to the CD, SD, IRB Chair, and OHSRP. This letter should be in Share Point as well as the personnel file of NIH and other Federal employees whose IRB service is part of their official duty (see 2.10.2 below)

Note: Nominees do not become a member of the IRB until they have received an appointment letter from the DDIR, although, at the discretion of the Chair, they may participate in IRB meetings prior to that time as consultants, consistent with the rules relating to such participation as a consultant (see 2.11).

F. Appointment Packet: The appointment packet to the DDIR includes:

1. Cover letter from the designated IRB (Appendix D in SOP 2);

2. Appointment letter for approval by the DDIR (Appendix C in SOP 2);

3. Nomination letter approved by the CD and SD, as applicable;

4. The nominee's *curriculum vitae;*

5. The signed "Statement of Status as Unaffiliated Member of an NIH IRB", as applicable (Appendix A in SOP 2);

6. The checklist of completed training (Appendix E in SOP 2);

2.5.2 Reappointment Procedures

A. IRB administrative staff are responsible for allowing enough time in advance of members' term end dates for the submission and processing of reappointment requests.

B. Reappointment letters: The Institute CD and SD make reappointment requests as applicable. The reappointment letter will be prepared and signed by the designated IRB and then submitted to OHSRP, which has delegated authority from the DDIR for approving such requests (see Appendix F in SOP 2) OHSRP will sign the letter and return it to the designated IRB for distribution to the member. Term lengths for reappointments (including of Chairs and Vice Chairs) can be for one, two or three years.

a. The signed letter will be sent to the member via the designated IRB confirming reappointment and will be copied to the CD, SD, and IRB Chair (see Appendix F in SOP 2).

C. Expiration of Terms: After the expiration of the term of an appointment, an individual is considered to be inactive as a member of the IRB and may not participate in IRB meetings (except as a consultant, according to the requirements at 2.11, below) until the reappointment letter from OHSRP has been signed.

2.5.3 Terms of Service

A. Unless reappointed, Chairs, Vice Chairs and members rotate off the Board when their terms expire and have not been renewed, when members tender their resignations, or when members are removed for cause.

a. Members who complete their term of service and are not reappointed will receive a Thank You letter from the DDIR. The designated IRB office will prepare the letter and submit it to the DDIR for signature. The DDIR will return the signed letter to the designated IRB. The signed letter will be sent to the member via the designated IRB and will be copied to the CD, SD, IRB Chair and OHSRP, (see Appendix G in SOP 2).

B. IRB Chairs, Vice Chairs and members may be reappointed in conformity with the rules stated in 2.5.2 above. There is no limit on the total number of years members may serve as a result of being reappointed multiple times, unless Institute management wishes to impose a limit.

C. Chairs and Vice Chairs may serve as regular IRB members on the same IRB or another NIH IRB after their terms as Chair and Vice Chair are completed.

2.11.4 Provision of Consultant Advice

A. The IRB administrative office ensures that the consultant understands his/her confidentiality obligations and receives a copy of the proposed protocol and any other supporting documentation in a timely manner.

SOP 3 – Management and Administrative Operations of the IRB
Version 2, 8-17-2015

3.2. Policy

NIH IRBs are expected to adhere to the basic requirements of this SOP but are allowed some flexibility in their operations and management in order to handle the wide range of clinical research activities conducted in the NIH's Intramural Research Program (IRP).

3.3. IRB Administrative Staff Responsibilities

3.3.1 IRB Administrative Office

Each NIH IRB has an Administrative Office. The title, number, grade level and responsibilities of the administrative support staff vary depending on the IRB's workload and research portfolio and are decided by appropriate Institute/Center (IC) leadership.

3.3.2 IRB Administrative Staff

IRB administrative staff who are employees of the individual Institutes or are contractors, are selected and appointed by the IC Scientific Director (SD) or Clinical Director (CD).

A. Each IC will designate a mechanism for supervision of the NIH IRB administrative staff.

B. IRB administrative staff members may not serve as a voting IRB member on the IRB that they administer.

3.4 IRB Administrative Staff Initial and Continuing Training and Educational Requirements

A. Initial and continuing educational requirements for IRB administrative staff are described in SOP 25 - Training Requirements for the NIH HRPP.

B. All IRB administrative staff members are encouraged to become professionally certified as IRB professionals (e.g. Certified IRB Professional - CIP) and to attend professional meetings.

3.5 The IRB Professional Administrators' Committee (IPAC)

As part of their continuing training requirements, IRB administrative staff members are expected to attend meetings of IPAC regularly in order to keep up to date on the latest developments in human subject research protections. The IPAC, founded in 2004, consists of IRB support staff and representatives from OHSRP and the Office of Protocol Services, and is dedicated to ensuring compliance with regulatory standards governing human subjects research by developing and promoting effective and consistent procedures and practices across the IRB offices. (See **References** in SOP 3 for the link to the OHSRP website and the IPAC mission statement and accomplishments.) The IPAC Chair is a voting member of the Human Research Subjects Advisory Committee (HSRAC).

A. Monthly meetings: A representative from the administrative staff of each NIH IRB is expected to attend the monthly meetings of the IPAC. Agendas for these meetings include exchange of information about the latest regulatory rulings, changes in NIH policies and procedures, sharing best practices, and other matters as appropriate.

B. Annual Retreat: IPAC holds an annual retreat, which all IRB administrative staff members are expected to attend.

3.6 IRB Resources and Facilities

Each IRB receives resources from the IC(s) it serves. Each IRB shall maintain a record of its resources, including the following information, which will be provided to OHSRP upon request:

A. Financial resources

B. Names, titles, and contact information for IRB administrative staff

C. Size and location of office

D. Computer equipment

E. Information technology support

F. Website, if applicable

G. Protocol management databases, and

H. Physical and electronic security to protect files and records

3.7 Protocol Submission Deadlines

Each IRB office establishes its own deadline for the submission of protocols, continuing reviews and amendments by PIs to the IRB for review. The IRBs will have a written statement with this information on file with OHSRP. This statement can be updated as needed.

3.8 Administrative Review of Submissions

3.8.1 Complete Submissions

IRB administrative staff verifies that all submissions to the IRB are complete. Incomplete submissions will not be reviewed by the IRB.

3.8.2 Required Elements for Each Type of IRB Submission

Required elements for each type of IRB submission are described in SOP 8 "Procedures and Required Documentation for Initial Review of Protocols by a Convened NIH IRB" and SOP 9 - Continuing Review by the Convened IRB, SOP 10 - Amendments to IRB-approved Research.

3.9. The IRB Meeting Agenda

The agenda is prepared by the IRB administrative staff in conjunction with the IRB Chair and must include the following, when applicable:

A. Announcements

B. Minutes of the Previous IRB Meeting (see SOP 4 - Human Research Protection Program (HRPP) Documentation and Records)

C. Reports of Expedited Actions

D. New Protocols for Review

E. Continuing Reviews

F. Amendments

G. Reports of Unanticipated Problems Requiring Full Board Review

H. Relevant Additional Items

3.9.1 Provision of Agendas to IRB Members

Agendas with accompanying attachments are provided to IRB members electronically or in hard copy at least 5 days before the IRB meeting. Copies of the agendas should be sent to OHSRP at the same time as they are distributed to members.

3.9.2 Attachments to Agendas

Attachments for the most common types of review are detailed below:

A. Initial Reviews: (See also SOP 8 - Procedures and Required Documentation for Submission and Initial Review of Protocols). At a minimum, all IRB members receive:

    1. The NIH Intramural Initial Clinical Protocol Application (this form is built into the applicable NIH IRB electronic system)

    2. The full protocol

    3. The proposed informed consent/assent document(s)

    4. Documentation of completed scientific review

    5. Recruitment materials (e.g. advertisements), if any

B. Continuing Reviews: (See also SOP 9 - Continuing Review by the Convened IRB). At a minimum, all IRB members receive:

    1. The NIH Intramural Clinical Protocol Continuing Review Application (this form is built into the applicable NIH IRB electronic system)

    2. Current consent/assent document(s)

    3. DSMB reports (if applicable)

    4. Annual reports to the FDA (when applicable, if requested by the IRB)

Note: A copy of the complete protocol, incorporating all amendments previously approved by the IRB is available for members' review at each IRB meeting. Upon request, all records, including relevant IRB meeting minutes, are available for any member for review prior to the meeting.

C. Amendments: (See also SOP 10 - Amendments to IRB-approved Research). At a minimum, all IRB members receive:

1. The NIH Intramural Clinical Protocol Amendment Application (this form is built into the applicable NIH IRB electronic system)

2. Revised protocol and consent documents (as applicable)

3. Any other relevant materials

D. Study Closure: (See also SOP 9 - Continuing Review by the Convened IRB). At a minimum, all IRB members receive:

1. The NIH Intramural Clinical Protocol Study Closure Application (this form is built into the applicable NIH IRB electronic system)

2. Any other relevant materials

3.10 Routing of IRB Documents After IRB Approval

IRB-approved documents are forwarded for approval/review and signature(s) as appropriate to the: IRB Chair or designee(s), IC Clinical Director, Office of Protocol Services (OPS), CC Director or the Deputy Director for Clinical Research.

3.11 Management of IRB Rosters and Nominations

The IRB Office shall maintain the IRB roster. The IRB office shall issue the nomination/appointment letters and maintain supporting documentation for appointed IRB members. The IC and IRB Chair will work together to ensure IRB member appointments satisfy regulatory and policy requirements specified in SOP 2 - IRB Membership and Structure. The IRB office shall:

A. Use the roster spreadsheet provided by OHSRP and as specified in SOP 2 - IRB Membership and Structure.

B. Maintain the IRB roster by keeping it current when new members are nominated and appointed, current members are renewed, or members leave.

C. Survey members regarding their self-designation of race, gender, institutional affiliation and representative capacity at time of appointment and no less than once a year.

D. Maintain rosters and the final documentation for the appointment of members in a shared location as specified by OHSRP and SOP 2 - IRB Membership and Structure.

E. Use the nomination and appointment letter templates provided by OHSRP and as specified in SOP 2 - IRB Membership and Structure.

F. Maintain documentation for the appointment of members in a shared location as specified by OHSRP and SOP 2 - IRB Membership and Structure.

SOP 4 – Human Research Protection Program (HRPP) Documentation and Records
Version 4, 10-21-2015

4.2 Policy

The NIH keeps adequate records of its IRBs' and the OHSRP's activities. These records may be on paper or in electronic format and are stored in the IRB administrative office or on NIH servers. IRB documents will be accessible for inspection and reproduction by the OHSRP, authorized representatives of the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), sponsors, and other NIH authorized entities. For FDA requirements regarding documentation and records, see SOP 15 - Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications.

4.3 Records Kept by NIH IRBs

4.3.1 Records Kept by the IRB Administrative Office

Records kept by the IRB administrative office include, but are not limited to:

A. IRB membership rosters (see 4.3.2, below)

B. IRB Research Protocol Files – All Protocols (see 4.3.3, below)

1. IRB Research Protocol Files –Additional documentation requirements for expedited reviews as specified by SOP 7A - Requirements for Expedited Review of Research by NIH Institutional Review Boards, including:

2. Documentation of IRB determinations for expedited actions in the IRB system (see 4.3.3.B, below)

C. Copies of IRB meeting agendas including the written lists of all actions approved by the expedited procedure

D. Copies of convened IRB meeting minutes (see 4.4, below, IRB Minutes)

E. Training records for IRB members and IRB administrative staff (see SOP 25 - Training Requirements for the NIH Human Research Protection Program (HRPP))

F. Records of IRB quality assurance and quality improvement (QA/QI) activities including QA/QI reports from internal and external site monitors/auditors and documentation related to non-compliance matters investigated by the IRB (see SOPs 16A - Allegations of Non-compliance with Requirements of the NIH Human Research Protection Program (HRPP) and 23 - Quality Management System for the NIH Human Research Protection Program (HRPP))

G. Institute-specific IRB operating procedures, if any, approved by OHSRP

4.3.2 IRB Membership Roster

Consistent with requirements set forth in SOP 2 - IRB Membership and Structure, NIH IRBs will maintain current membership rosters, report membership changes as they occur to OHSRP and verify roster information annually.

4.3.3 IRB Research Protocol Files

A. All Protocols: The IRB will keep a separate file for each research study that is received for review. Each research protocol will be assigned a unique identification number and entered into an IRB tracking system. Each research study file must include the following minimum information, if applicable:

1. Initial Review (IR) application and all related documents (including informed consent forms), for more information see SOP 8 -Procedures and Required Documentation for Submission and Initial Review of Protocols

2. All IRB-approved, dated versions of the protocol

3. Documentation of scientific review or deferral of this requirement by designated Institute officials

4. For research involving FDA regulated drugs, the Investigator's Brochure is kept per 4.7 below

5. For research involving FDA regulated devices, required documentation is provided and kept (see SOP 15 - Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications)

6. Continuing review (CR) application and all related documents (see SOP 9 - Continuing Review by the Convened IRB)

7. Amendments to the research protocol and all related documents (see SOP 10 - Amendment to IRB-approved Research. Reports of Unanticipated Problems, Adverse Events and Protocol Deviations)

8. Problem Report Forms including reports of unanticipated problems (UPs), protocol deviations and non-compliance (see SOP 16 - Reporting Requirements for Unanticipated Problems, Adverse Events, and Protocol Deviations)

9. Fully executed Authorization/Reliance agreements that rely upon the NIH IRB

10. Material Transfer Agreements (MTAs), including human Material Transfer Agreements (h-MTAs); Cooperative Research and Development Agreements (CRADAs); or other human subjects agreements if provided by the PI

11. Advertisements or recruiting materials

12. IRB-approved PI communications that convey significant new findings or other information to subjects

13. Documentation of all IRB review actions (See 4.4 IRB Minutes) including the approval period

14. Documentation pertaining to Data Safety and Monitoring Board reports

15. Documentation pertaining to audits, investigations, reports of monitoring visits relating to specific protocols, if provided by the PI

16. All other IRB correspondence with the investigators, and with any other relevant entities associated with the research (See SOP 7 - Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting for more details). Examples include the IRB approval letter with any attachments or requests to the PI for more information and including copies of stipulations describing what is required of Principal Investigators in order to conduct the study.

B. Documentation for Expedited Reviews: IRB actions through expedited procedures must be consistent with requirements set forth in SOP 7A - Requirements for Expedited Review of Research by NIH Institutional Review Boards (IRBs).

4.4 IRB Minutes

4.4.1 Federal Requirements for The Content of IRB Minutes

45 CFR 46.115(a)(2) provides minimal requirements for the content of IRB minutes:

A. Minutes of the IRB meetings shall be in sufficient detail to show attendance at the meeting

B. Actions taken by the IRB

C. Any determinations required by the regulations including protocol-specific findings supporting those determinations

D. The record of IRB votes on all voting actions (e.g., IRs, CRs or UPs) including the number of members voting for, against and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution

4.4.2 Preparation of IRB Minutes

The minutes may be prepared by the IRB office staff or by a contractor hired for the purpose. The draft minutes must be reviewed by the IRB Chair/designee prior to the distribution of stipulations to investigators. Final approval of the minutes will be voted up on by the IRB.

Proceedings from the IRB meeting will be documented in the meeting minutes and available for review at the next regularly scheduled IRB meeting. Once approved by the IRB, the minutes can no longer be revised or altered. Any subsequent corrections may be done through a documented IRB action and the information appended to the minutes. A copy of the IRB-approved minutes will be provided to the Institutional Official (IO) and other authorized officials upon request.

4.4.3 Format for IRB Minutes

The recommended NIH format for minutes (see Appendix A in SOP 4) may be downloaded from OHSRP's website (see List of Links below).

Note: This format is recommended for use by all NIH IRBs, but an NIH IRB may develop its own format as long as the required core elements contained in Appendix A in SOP 4 are included.

4.4.4 Content of IRB Minutes

Minutes of IRB meetings must include the following:

A. Meeting date, location, Chair presiding, time meeting convened with a quorum, time adjourned

B. Attendance

1. Names of the primary and alternate members who are present and absent at the beginning of the meeting identifying their status (as scientists, non-scientists, unaffiliated, etc. consistent with requirements set forth in SOP 2 - IRB Membership and Structure. When alternates attend, the minutes will state the name of the primary member for whom they are substituting and the reason for their attendance (e.g., the primary member is absent, or is recused).

2. The minutes should document the name and status of members who attended any part of the IRB meeting, in-person or by videoconference or teleconference.

3. Names of primary and alternate members who are participating through videoconference or teleconference. Documentation that they received all pertinent material prior to the meeting and were able to participate actively in all discussions. For more information, see SOP 3 - Management and Administrative Operations of the IRB and SOP 7 - Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)

4. Name(s) of IRB administrative staff, OHSRP staff, and any consultants and/or guests present

5. Name(s) of investigators present

C. Review and vote on the minutes from the previous meeting

D. Announcements and informational items

E. Documentation of the quorum and voting: The presence of a quorum throughout the meeting must be reflected in the minutes, including the presence of one member whose primary concern is in a non-scientific area. The minutes will indicate, by name, those members who are absent, abstaining or recused for each vote during the meeting. There will be a notation in the minutes that a member's recusal occurs because of a conflict of interest. Also see Appendix A -Recommended Format for All NIH IRB Minutes, re: Conflict(s) of Interest in SOP 4.

F. In order to document the continued presence of a quorum, each research study reviewed must have a record of the number of votes including which members were present, absent, abstained or recused for conflict of interest, as follows:

(a) Total #: For (#), Against (#), Abstained (#)
(b) Recused (#; name), Absent (#; name)

G. Review of interim reports, e.g. unanticipated problems: protocol violations/deviations; serious or continuing 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)); suspensions/terminations, etc. (see SOP 11) and corresponding IRB determinations

H. For the review of previously deferred protocols, new protocols, amendments and continuing reviews, the following must be recorded:

1. PI name, protocol number, and complete protocol title

2. Determinations of whether or not the IRB Protocol Review Standards are met (see SOP 7 - Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs))

3. Discussion and deliberations of controverted issues and how they are resolved

4. Evaluation by the IRB of the required elements of 45 CFR 46.111

5. Actions taken by the IRB, including separate deliberations and votes on each action including the basis or justification for these actions

6. Designating who will review and approve the PI's response to stipulations (e.g., the full committee, a subcommittee, or by the Chair)

7. Approval period for initial and continuing approved protocols, including identification of research that warrants review more often than annually and the basis for that determination

I. Documentation of Specific Findings: Findings of the IRB, and the protocol-specific information justifying these findings, must be recorded in the minutes. These may include, but are not limited to, the following:

1. Alteration or waiver of requirements for informed consent: When approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain informed consent, protocol-specific documentation that the research meets the required criteria (45 CFR 46.116(d))

2. Waiver of requirements for written documentation of informed consent: When the requirements for written documentation of consent are waived, protocol-specific documentation that the research meets the required criteria (45 CFR 46.117(c))

3. Research involving vulnerable subjects: When approving research that involves populations covered by 45 CFR 46 Subparts B (pregnant women), C (prisoners), or D (children), the minutes will document the IRB's justifications and findings that regulatory requirements are met or its agreement with information and justifications as provided by the investigator (e.g., whether the signature of one parent is sufficient to enroll a child in research). When the research may involve other groups that are likely vulnerable to coercion or undue influence such as mentally disabled persons or economically or educationally disadvantaged persons, the IRB should document additional safeguards have been included in the study to protect the rights and welfare of these subjects.

4. Research involving adults who are or may be unable to consent: Document that NIH requirements are satisfied (see SOP 14E - Research Involving Adults Who Are or May be Unable to Consent)

J. The rationale for significant risk/non-significant risk device determinations (See SOP 15B - Research Regulated by the Food and Drug Administration (FDA): Information and Policies for Investigational Device Exemptions (IDE) Applications)

K. Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research, see SOP 7 - Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs).

L. Documentation that the IRB went into executive session (when applicable), see SOP 7 - Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting.

4.7 Protection of and Access to IRB Records

NIH IRBs must protect the confidentiality of research information:

A. All IRB paper records are kept secure in locked filing cabinets or locked storage rooms. Doors to offices where IRB records are kept must be closed and locked when the rooms are unattended.

B. Electronic IRB records are maintained according to applicable laws, regulations and NIH policies and procedures for computer and electronic record security.

C. Subject to applicable law and Federal policy, access to IRB records is limited to the Institute Clinical Director, the IRB Chair, IRB members, the IRB staff, authorized NIH and OHSRP officials, and officials of Federal regulatory agencies (OHRP, FDA, etc...). Appropriate accreditation bodies may be provided access to IRB records as needed.

D. Research investigators may be provided reasonable access to IRB files related to their protocol(s). The IRB Chair or Institutional Official will determine if research investigators should be allowed to view IRB records (and to what extent). This determination will be based on documentation of a legitimate need and made in accordance with applicable laws and regulations.

E. Records may not be removed from the IRB office; however, the IRB staff will provide copies of records or access for inspection if copying is not permitted by authorized personnel (see a description of authorized personnel in paragraph 4.7.C).

4.8 Record Retention

IRB records will be retained for at least three (3) years after completion of the research. IRB records not associated with research or protocols cancelled without participant enrollment will be retained at least 3 years after closure. After that time, IRB offices and OHSRP will comply with NIH Manual Chapter 1743 - Keeping and Destroying Records (see **References** in SOP 4).

SOP 7 – Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Board (IRBs)
Version 3, 8-7-2015

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.

7.5.2 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.

7.17 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.

SOP 7A – Requirements for Expedited Review of Research by NIH Institutional Review Boards (IRBs)
Version 3, 8-4-2015

7A.2 Policy

Research activities that satisfy 45 CFR 46.110 and 21 CFR 56.110 (when applicable), may be reviewed through the expedited review procedure. Like review by the convened IRB, expedited review must fulfill all the requirements of review found at 45 CFR 46.111 and subparts B, C, and D, if applicable.

7A.5 Procedures for Review of Research Activities by The Expedited Process

A. Pre-review of Research Activities for Expedited Review: The IRB staff, in consultation with the IRB Chair or designee, pre-reviews all submissions for expedited review, including applications for expedited initial review, expedited continuing review, expedited closure of protocols, and expedited amendments for minor changes to previously approved research. The determination of whether an item is eligible for consideration under the expedited review procedure is made by the IRB Chair or designee. The decision whether to expedite eligible items or to send them for full Board review is at the discretion of the IRB Chair or designee.

B. Selection of Reviewers for Research Activities Eligible for Expedited Review:

    1. The IRB Chair, or one or more experienced IRB members designated by the Chair, may review and approve research that meets criteria for expedited review.

    2. An experienced IRB member is defined as a regular or alternate member who knows the expedited review categories, and, in the judgment of the Chair, possesses the expertise needed to review the proposed research.

C. Responsibilities of Reviewers

    1. Reviewers may obtain additional consultation.

    2. Reviewers may approve submissions unconditionally or approve with stipulations but may not disapprove research.

        a. If the reviewer determines that the research is not eligible for expedited review, or even if eligible for approval by expedited review but should still be

reviewed by the convened IRB, this recommendation will be forwarded to the IRB Chair for non-expedited review by the convened IRB.

b. If the reviewer determines expedited review is appropriate for the research, the reviewer will determine a review interval for approved expedited research not less than once per year (see SOP 7 - Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs).

c. Any stipulations that must be met prior to final approval of expedited research are sent to the investigator by mail or email and documented in the IRB file. Final approval is provided by the IRB Chair or designee when the response to stipulations has been submitted and approved by the designated reviewer.

7A.9 Reporting and Documenting IRB Actions Regarding Expedited Review.

A. The reviewer of expedited actions documents determinations in the IRB system per Appendix A in SOP 7A, including the specific expeditable category or categories relevant to the action.

B. IRB members are provided with a written list of all actions approved by the expedited procedure in the next meeting agenda. IRB members may request additional information.

C. The IRB will provide the PI with the outcome of expedited review.

D. Expedited review actions announced at a convened IRB meeting are listed in that meeting's IRB minutes.

E. The expedited actions are entered and tracked in the IRB and Office of Protocol Services (OPS) databases in the same way as non-expedited actions.

SOP 8 – Procedures and Required Documentation for Submission and Initial Review of Protocols
Version 4, 1-12-2016

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

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.

9.2 Policy

Consistent with 45 CFR 46.109(e), and OHRP "Guidance on IRB Continuing Review of Research", dated November 10, 2010, (see **References** in SOP 9), NIH IRBs shall conduct CR of human subjects research at intervals appropriate to the degree of risk, but not less than once per year.

When conducting CR, the IRB should start with the working presumption that the research, as previously approved, does satisfy all of the regulatory criteria. The IRB should focus on whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB's prior determinations, particularly with respect to the IRB's prior evaluation of the potential benefits or risks to the subjects. The IRB also should assess whether there is any new information that would necessitate revision of the protocol and/or the informed consent document.

9.6 CR Submission Materials

An IRB staff member, or a designee, will review each IRB submission package to determine that each of the required items has been submitted.

A. Timing: Investigators should not submit CR materials too far in advance of the CR expiration date but with enough time prior to the expiration date to ensure time to respond, if needed, to any stipulations/conditions.

B. Materials: The PI must submit the following materials for CR except when the research satisfies expedited CR category 8(c) authorized by 45 CFR 46.110 (see 9.6.1 below): procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110

    1. A completed "NIH Intramural Clinical Research Protocol Continuing Review Application" using the designated IRB submission system.

    2. The current IRB-approved, dated protocol, if changed from the previous year, with version number, page numbers, and all amendments incorporated.

    3. The current IRB-approved informed consent/assent document(s), unless enrollment is complete.

    4. If the PI intends to close the study, an Intramural Clinical Protocol Study Closure Application (submitted in the designated IRB system). For more information, see SOP 11A - Closure of an IRB-approved protocol.

    5. The IC-approved Cumulative Inclusion Enrollment Report (CIER), (see SOP 13 - Recruitment, Selection and Compensation of Research Subjects).

6. Any data and safety monitoring reports for the last review period, such as Data and Safety Monitoring Board (DSMB) or Committee (DSMC) reports, as applicable (see SOP 17 - Data and Safety Monitoring).

7. Most recent Annual Report to the FDA (e.g. IND annual Report), as applicable (see SOP 15A - Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products).

8. Amendments to the protocol may accompany the CR submission but must be reviewed and approved separately. The separate vote approving the amendment must be documented in the Minutes of the IRB consistent with the requirements of SOP 4 - Human Research Protection Program (HRPP) Documentation and Records.

9. Aggregated summary reports, as follows (numbers a-e, below, are also referenced in SOP 16 - Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations regarding event reporting duties):

    a. All Unanticipated Problems (UPs).

    b. All Protocol Deviations (except those expected Protocol Deviations granted a waiver in the protocol - unless it is also a UP).

    c. All Unanticipated Adverse Device Effects (UADE)

    d. All Adverse Events (AEs) (including expected AEs, except those specified in the protocol and approved by the IRB as not reportable, i.e., granted a waiver, unless it has been determined by the PI or IRB that they are also UPs).

    e. While preparing the CR Application, the PI must assess whether expected AEs are occurring at greater frequency or severity than previously expected. If this occurs, the aggregate information may also qualify as a UP and must be reported as such (See SOP 16 - Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations).

    f. Any information in the literature, or evolved from similar research, that might affect the IRB's analysis of risk/benefit for the protocol. If such information is obtained before the time of CR, it should be reported to the IRB at the time that it becomes known, and summarized at the time of CR.

    g. A summary of any research-related complaints from subjects.

9.12.3 IRB Approval with Stipulations

An IRB has authority to approve research with stipulations. When research is approved at CR with stipulations, the PI generally has thirty days to respond the stipulations. The thirty days is counted from the date the PI is notified of the stipulations. An IRB has discretion to give a PI more than thirty days to respond to stipulations, consistent with this policy.

Research is not considered to have lapsed if the research is approved with stipulations before the expiration date and final IRB approval is obtained no more than thirty days after the expiration. The research is considered lapsed if stipulations are not approved by the IRB within 30 days after the expiration date. If an IRB approval with stipulations crosses over the expiration date, PIs should respond quickly to these stipulations to avoid a lapsed protocol.

If an IRB approves a CR with stipulations that go beyond the expiration date, the IRB must promptly inform OPS of the IRB decision and either instruct OPS to extend the expiration date on a reposted consent document, or provide a new consent to be posted.

9.13.2 Actions at Other Sites other than the CC when an NIH IRB is the IRB of Record

For expired protocols conducted at sites other than/or in addition to the Clinical Center, the IRB office:

A. Notifies the PI that human subjects research, consistent with the requirements outlined in Section 9.12.1 above, must cease, and

B. Notifies OHSRP and the IC Clinical Director that the protocol has expired.

SOP 10 – Amendments to IRB-Approved Research
Version 3, 2-24-2016

10.2 Policy

PIs are responsible for obtaining IRB approval of proposed amendments to an IRB-approved protocol before implementing them. The only exception to this requirement is when a change is necessary to eliminate apparent immediate hazards to subjects (see 45 CFR 46, see References in SOP 10 and SOP 19 - Investigator Responsibilities).

10.4 Procedures for IRB Review and Clinical Director (CD) Review of Protocol Amendments

A. Administrative Pre-review of Protocol Amendments: The IRB administrative staff may pre-review amendment requests to assist the IRB chair to determine if the

investigator submitted all necessary information. Pre-review may also be used to determine whether the amendment would be a minor change to the research and may be eligible for expedited review (see SOP 7A - Requirements for Expedited Review of Research by NIH IRBs).

B. Expedited Review of Amendments: If the Chair or designee decides that the amendment is eligible for expedited review, it is reviewed according to SOP 7A - Requirements for Expedited Review of Research by NIH Institutional Review Boards.

C. Review of Amendments by the Convened IRB:

9. All IRB members receive all the submitted amendment materials and will have access to the complete IRB protocol.

10. IRB members must review the provided materials in order discuss them and vote at the meeting.

11. The IRB Chair may assign an IRB member to perform a primary review of the amendment and lead the discussion at the IRB meeting.

12. In reviewing the proposed amendment, the IRB should consider how it will affect the conduct of the study; whether it meets the regulatory criteria for approval (45 CFR 46.111); and whether or not it can be approved as written based on the IRB's risk/benefit assessment.

13. The IRB can take the following actions on amendments: unconditional approval, approval with stipulations, deferred approval, tabled or disapproved, as described in SOP 7 - Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs).

14. The IRB will document in the minutes its discussion about and vote on the amendment and its determination whether current or past subjects must be informed of the amendment, and, if so, how they will be informed (verbally and/or in writing). Current and past subjects must be notified if the study amendment affects their safety and welfare and current subjects re-consented if the amendment changes future clinical study procedures. Correspondence or other communications with subjects shall be submitted to and approved by the IRB.

15. The IRB votes separately on new amendments that accompany continuing reviews.

16. Clinical Director signatures/approvals are not required on all amendments. Each CD has authority to decide which IRB actions require CD approval, and they should communicate that information to the IRBs and to the CC Office of Protocol Services (OPS).

SOP 11 – Suspension and Terminations of IRB Approval and Administrative Holds
Version 3, 9-4-2015

11.11 Administrative Hold

An investigator may institute an administrative hold on a study when he/she wishes temporarily to stop, or as a preliminary step before permanently stopping, some or all approved research activities. An administrative hold may be in response to a directive from a sponsor, or FDA or other authorized review body. Senior NIH officials, such as the Institute Director/Clinical Director or Director, Clinical Center, may request an administrative hold for NIH institutional reasons, e.g., loss of funding, departure of the PI from NIH.

Administrative holds are not suspensions or terminations, and are not an IRB directive requiring notification to OHRP, but the IRB needs to be notified of administrative holds to ensure that the rights and welfare of subjects are protected. Studies on administrative hold require continuing review by the IRB prior to the expiration date. The procedures for initiating and implementing an administrative hold are:

H. The Principal Investigator must notify the IRB in writing within five days of the action that he/she is voluntarily initiating an administrative hold on the study.

I. The administrative hold notification is submitted as an amendment and must include a description of the research activities that will be put on hold.

J. A justification for the administrative hold and any supporting documentation that include the proposed actions to protect and notify currently enrolled subjects.

Upon receipt of written hold notification, an administrative hold notice is treated as an amendment to the previously approved research using the protocol review standards for amendments. (See SOP 7 – Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)). The amendment may receive expedited review, if applicable. The IRB staff includes the request on the IRB meeting agenda for review.

K. The IRB Chair or the convened IRB reviews the hold actions and determines whether any additional procedures need to be followed to protect the rights, safety and welfare of currently enrolled subjects.

L. The IRB Chair or the convened IRB notifies the PI of any additional procedures that need to be followed to protect the rights, safety and welfare of currently enrolled subjects.

M. The IRB will notify the IC and, where applicable, the CC, Office of Protocol Services (OPS), in writing, of what activities, if any, are authorized to continue and conditions for such continuation. The IRB should indicate if the current consent form should remain posted or not.

N. When the entire protocol is placed on administrative hold, the accrual status changes to "Clinical Hold/Recruitment or enrollment suspended" in OPS. On clinicaltrials.gov the status will appear as suspended, which indicates that participant recruitment and enrollment has halted but potentially will resume.

SOP 22 – Research Subject Information and Services and Research-Related Complaints from Research Subjects
Version 2, 8-13-2015

22.2 Policy

The NIH's human research protection program (HRPP) has procedures in place to provide information and services to research subjects. The HRPP also ensures that complaints about participation in research are given serious consideration and that efforts are made to identify and resolve such complaints.

22.4.2 Lodging Complaints

A. Research subjects may bring their problems or complaints *regarding their participation in research* to the attention of Principal and/or Associate Investigators (PIs or AIs) or other health care/research staff (e.g., nurses, social workers); OHSRP staff; the NIH IRB Chair and/or IC or other NIH officials. In addition, at the CC, subjects may contact the Department of Bioethics and/or the CC Ethics Committee, and the CC Patient Representative. At non-CC sites, complaints also may be referred to an IC Compliance Office.

B. Issues or complaints related to the quality of clinical care and/or patient safety related concerns at the CC should be directed to the Office of the Deputy Director for Clinical Care (DDCC) or to comparable persons/entities for research conducted at non-CC NIH sites.

C. Complaints that deal with concerns unrelated to research or patient safety/clinical quality, e.g., quality of food, parking problems, etc., are referred to appropriate entities such as the CC Office of the Chief Operating Officer, the CC Department of Social Work and/or the CC Patient Representative or to comparable persons/entities for research conducted at non-CC NIH sites.

22.4.3 Documenting Complaints

Complaints, written or verbal (including telephone complaints) will be documented and kept on file by the recipient (e.g., the PI, the Patient Representative) and in the relevant receiving office (e.g., the IRB administrative office, the OHSRP, the Office of the DDCC, the IC Compliance Office) consistent with applicable laws for privacy. If a complaint related to research participation is received initially by OHSRP, the appropriate IRB Chair and the PI of the relevant protocol will be notified, as appropriate.

A. Generally, the following information will be documented as applicable:

1. Subject's (or complainant's) name, address, and phone number, if provided

2. Protocol title/number and the name of the PI

3. Date(s) of the incident if known, and

4. An explanation of the concern, complaint, or question

B. Anonymous reports are accepted. However, the person receiving the complaint may need to advise the complainant that the inability to follow-up to gather more information may hinder an investigation and that the results of an investigation and/or the provision of follow-up information may not be possible (see Section 22.4.6).

C. The name of the complainant(s) will be kept confidential to the extent possible. Complainants may be advised that complete confidentiality cannot always be maintained during an investigation.

SOP 26 – Evaluation of NIH IRB Chairs, Vice Chairs and Members, IRB Administrative Staff and IRB Committee Activities
Version 3, 6-9-2016

26.2 Policy

NIH officials conduct periodic evaluations of IRB Chairs and Vice Chairs, IRB members, IRB activities and IRB administrative staff to assure that the NIH IRBs comply with regulatory requirements and the NIH HRPP SOPs, and to identify areas that need improvement, and to justify changes, when needed.

26.5 Evaluation of NIH IRB Administrative Staff

A. IRB administrative staff members are employees of the individual Institutes or are contractors. Each IC will designate a mechanism for supervision and at least an annual evaluation of the NIH IRB staff. For NIH employees, this would be the employee's HHS Employee Performance Plan (Form HHS-704B).

B. Standards and responsibilities may include, but are not limited, to those listed in Appendix D in SOP 26.