Guideline for Investigator Responsibilities when Conducting FDA-Regulated Research and NIH is the Reviewing IRB

(Also see Policy 300 *Investigator Responsibilities*; Policy 500 *Research Involving Drugs, Biological, and Nutritional Products*; and Policy 501 *Research Involving FDA Regulated Devices*)

Responsibilities before the research begins:

- Obtain scientific review from PI's IC prior to submission to the IRB. (See this OHSRP resource regarding scientific review.)
- In collaboration with IC leadership, the PI should ensure sufficient resources exist to conduct the research (e.g., access to subjects, time to conduct and complete research activities, adequate staff and facilities).
- Complete required education and ensure training of research staff. (See Policy 103 *Education Program.*)
- Comply with NIH requirements for reporting and disclosure of conflicts of interest. (See Policy 102 *Institutional and Investigator Financial Conflict of Interest in Human Subjects Research*.)
- Provide a protocol document with sufficient information for IRB review (see *Templates and Forms*). The protocol is the "recipe" to be followed by the research team.
    - For multi-site research, see *Reliance Resources*.
    - When the research involves the clinical investigation of a test article, provide documentation in the protocol whether the test article(s) for use is under an IND or provide written justification for why the test article(s) is exempt from the requirement for an IND (21 CFR 312.2). (See FDA guidance, Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND, September 2013.)
    - If the use of the test article (drug or biologic) is not exempt from the requirement for an IND, the PI is responsible for providing documentation to the IRB confirming that an IND is in effect prior to review of the protocol by the IRB. (See Policy 500 *Research Involving Drugs, Biological, and Nutritional Products.)*
    - Include either the Package Insert (in the case of an approved drug) or Investigator Brochure (IB) if one exists, with protocol submission to the NIH IRB. If no IB exists for an investigational drug, the investigator must include in the protocol all relevant preclinical and clinical safety and efficacy data to support the proposed use of the test article in the research.
    - When the research involves the study of the safety or efficacy of an investigational device, provide documentation supporting the sponsor's assessment of whether the device is exempt (21 CFR 812.2(c)), nonsignificant risk (NSR) or significant risk (SR) to the reviewing IRB. (See Policy 501 *Research Involving FDA Regulated Devices*.)

- Obtain IRB approval of the protocol and other study materials (e.g., recruitment materials), as appropriate, and any required ancillary committee approvals. (See Policy 106 *Ancillary Reviews* and, for recruitment information, see Policy 302 *Subject Recruitment and Compensation* and *OHSRP Recruitment Information Sheet*.)
- If applicable, ensure that contracts for CRADAs and other required clinical trial agreements have been fully executed before enrolling subjects.

Responsibilities during the conduct of the research:

- Maintain a regulatory file with current and accurate records of all study documentation as required by applicable regulatory requirements. (See NIH Manual Chapter 1743 – *Managing Federal Records*, the *NIH Intramural Records Retention Schedule*, and the *NIH Privacy Act Policy*.)
- The NIH PI may assign responsibility for specific aspects of the conduct of the research to appropriately qualified individuals consistent with the IRB-approved protocol and the NIH policy requirements (See Policy 300 *Investigator Responsibilities*.) However, at all times the PI retains overall responsibility for the conduct of the research and must ensure both the protocol and the research team's actions are compliant with law, regulation, and policy.
- Train the study staff about how to implement the protocol (at the beginning and with each amendment as the study progresses) and maintain documentation of this training in the regulatory binder.
    - Include information about recruitment, and how recruiting of subjects should be conducted and responsibility for recruitment.
- For research requiring signed consent (which also refers to parental permission in this document) or assent, obtain and document informed consent/assent using the current NIH IRB approved consent/assent documents. (See Policy 301 *Informed Consent*.)
- Conduct research in compliance with the final IRB approved protocol, the signed agreement with the sponsor, the investigational plan, and applicable FDA regulations and submit any changes to the research (protocol or other study materials) for review and approval by the IRB prior to implementation.
    - OHRP regulations at 45 CFR 46
    - FDA regulations 21 CFR 50 and 21 CFR 56 and "Guidance for Industry – Investigator Responsibilities"
    - other applicable regulations and policies that apply to the research including NIH HRPP policies
- Oversee (or delegate as appropriate) the control of drugs, biologics or medical devices as required by FDA: For drugs or biologics (21 CFR 312), or for devices (21 CFR 812). For research with investigational devices, use of the device must be limited to subjects under the investigator's supervision

- For research requiring signed consent (which also refers to parental permission in this document) or assent, obtain and document informed consent/assent using the current NIH IRB approved consent/assent documents. (See Policy 301 *Informed Consent*.)
- Maintain adequate and accurate subject study records and documentation to demonstrate compliance with the IRB-approved protocol; changes should be traceable, should not obscure the original entry, and should be explained, if necessary (e.g., single-line through the original entry, and initialed and dated).
- Ensure the subject's questions, concerns, and complaints are properly addressed and resolution documented and retained in the study record. Report these per Policy 104 *Research Related Subject Complaints*
- Report research-related events per Policy 801 *Reporting Research Events*, Policy 802 *Non-Compliance in Human Subjects Research* and the *Guidance: Reporting Research Events and Non-compliance*.
- Ensure all FDA safety reporting requirements are met as well as other required reports to the Sponsor (e.g., annual reports, final reports, and financial disclosure reports). (21 CFR 312.64) (See Policy 500 *Research Involving Drugs, Biological, and Nutritional Products* and Policy 501 *Research Involving FDA Regulated Devices*)
- Ensure the approved data and safety monitoring plan in the IRB approved protocol is followed and documented, including timely submission of reports, as applicable, per Policy 503, *Data Safety and Monitoring*.
- During the course of the research, updated IBs must be provided to the IRB within 7 days of receipt if the changes to the IB reflect, in the investigators judgment, an increase in risks to subjects or decrease in the acceptability of risks, or within 30 days of receipt if the changes do not adversely impact risk-benefit.
- Submit Progress Report Forms for Continuing Review (CR) submissions, study closures and for institutional "check-in" required for protocols that have been determined by the IRB to not require CR. For those studies requiring continuing review, ensure **timely** submission of the progress report (4 to 6 weeks prior to study expiration is recommended) to ensure continued IRB approval during the conduct of the study. If IRB approval expires, ensure all research activities are stopped, including recruitment, enrollment, interventions, interactions, and data analysis on current subjects. For those studies that **do not** require continuing review, ensuring **timely** submission of the Progress Report Form (within 30 days of the due date is recommended).
- Cooperate with any FDA inspections must provide to the OHSRP office of Compliance and Training a copy of all FDA Form 483s issued regarding an NIH research study.
- For clinical trials subject to the 2018 Common Rule, if the NIH is the only site, or in the case of multi-center research when NIH is the lead site, then the NIH PI, or the PI's Institute or Center (IC), must post one blank copy of an IRB-approved informed consent document used to enroll subjects in the research on a publicly available federal website that is established as a repository for such informed consent documents (e.g., ClinicalTrials.gov or Regulations.gov). The document must be posted after the trial is

closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

- If departing the NIH and research activities are continuing at the NIH, the PI should revise the protocol and obtain IRB approval of a new PI who is suitably qualified to be responsible for the conduct of the research prior to their departure.

Responsibilities after research is complete:

- Submit a final Progress Report Form to the IRB when a study is being closed.
- As applicable, ensure the submission of study results on www.ClinicalTrials.gov consistent with regulatory requirements as noted above.
- Follow record retention requirements such that at the closure of the trial, the Investigators and Sponsors retain the records and reports required for the longest of the following intervals: 1) at least 3 years as required by the NIH Manual Chapter 1743-3000 Records Retention; 2) two years after a marketing application is approved for the drug or, 3) if an application is not approved for the drug, records must be maintained for 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been notified
- If new information or findings related to subject safety or welfare are identified after a study has closed, provide the IRB with a report of the new information/findings.