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OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

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SOP Title: RESPONSIBILITIES WHEN THE NIH INTRAMURAL RESEARCH PROGRAM SERVES AS A COORDINATING CENTER FOR A MULTI-SITE TRIAL OR SERVES AS THE IRB OF RECORD FOR A NON-NIH COORDINATING CENTER

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

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TABLE OF CONTENTS

20C.1 PURPOSE 1

20C.2 POLICY 1

20C.3 DEFINITIONS 1

20C.4 INTRODUCTION 3

20C.5 PI RESPONSIBILITIES 3

20C.6 COORDINATING CENTER RESPONSIBILITIES..... 3

20C.7 IRB RESPONSIBILITIES WHEN REVIEWING PROTOCOLS FOR WHICH THE NIH WILL SERVE AS THE COORDINATING CENTER 6

20C.8 IRB RESPONSIBILITIES WHEN REVIEWING PROTOCOLS FOR WHICH A NON-NIH SITE WILL SERVE AS THE COORDINATING CENTER 7

SOP 20C - RESPONSIBILITIES WHEN THE NIH INTRAMURAL RESEARCH PROGRAM SERVES AS A COORDINATING CENTER FOR A MULTISITE TRIAL OR SERVES AS THE IRB OF RECORD FOR A NON-NIH COORDINATING CENTER

20C.1 PURPOSE

This SOP describes the responsibilities of the PI, NIH IRB and an NIH Coordinating Center when the NIH Intramural Research Program (IRP) serves as a Coordinating Center for the operation of a multisite trial, and the Coordinating Center is engaged in non-exempt human subjects research. (Occasionally data management may be conducted by another site or entity.) The SOP also addresses NIH responsibilities when an NIH IRB serves as the IRB of Record for a non-NIH Coordinating Center.

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.3 DEFINITIONS

- A. **Coordinating Center (Entity) for Multisite Studies:** A Coordinating Center is the entity that is responsible for overall planning, document collection, monitoring and communication among all sites participating in a multisite research project. A Coordinating Center may also be responsible for data management and analysis and may be designated either by a sponsor or by

- mutual agreement of the participating sites. The sponsor may delegate some of its responsibilities to the Coordinating Center as **in this SOP.**
- B. Executive Committee (for a Coordinating Center):** A group of individual leaders associated with the study that directs the study and ensures implementation and coordination of strategic plans for the research. The Committee participants vary based on the needs of the study. In the case of multisite studies, this Committee may be comprised of the Lead PI overseeing the implementation of the protocol, the PI of the Coordinating Center and the director of the Steering Committee.
- C. Federalwide Assurance (FWA):** A Federalwide Assurance is a written commitment by an institution to comply with the **protection of human subjects regulations** of 45 CFR 46. The FWA is filed with the DHHS Office for Human Research Protections **(OHRP).**
- D. Medical Monitor:** The medical monitor is a health care professional capable of overseeing the progress of the research protocol, especially issues of individual subject/patient management and safety. The medical monitor must be independent of the investigative team and possess sufficient educational and professional experience to serve as the subject/patient advocate. Depending on the nature of the study, the medical monitor may be assigned to assess one or more phases of a research project.
- E. Multisite Protocol (Multisite Research):** Multisite research/protocols refer to projects that will be conducted at more than one **Performance Site.** Usually a multisite study involves conduct of a protocol carried out at more than one medical institution or site. Sites may also include schools, nursing homes, community rehabilitation facilities, private practices, individual homes, etc. As part of the protocol application, the investigator shall disclose the entity that will serve as the Coordinating Center for the project.
- F. Performance Site (Enrollment Site):** A performance site, or an enrollment site, is a place where human subjects participate in research activities (e.g. often a clinic or hospital). The performance site's location may be different from the location where the IRB review occurs. Subjects are usually enrolled or followed at performance sites.
- G. Statistical Center:** Team of biostatisticians and others who provide statistical support from study design through data analysis and publication. A Statistical Center may also include database developers, data managers, regulatory

staff and administrators who provide infrastructure support for multicenter clinical trials.

20C.4 INTRODUCTION

When the NIH Intramural Research Program funds multisite research, it normally establishes Coordinating Centers to fulfill responsibilities for oversight activities, including data and safety monitoring. If a Coordinating Center is not established, the funding NIH Institute/Center is responsible for ensuring that oversight activities occur, including establishing GCP monitoring programs, if required pursuant to the FDA regulations.

20C.5 PI RESPONSIBILITIES

It is the responsibility of the PI for a Coordinating Center to develop a protocol that describes the non-exempt human research activity of **the** Coordinating Center. During the period of IRB approval, the PI should file an amendment to the Coordinating Center protocol regarding any changes in the Coordinating Center's standard operating procedures that are related to issues below.

20C.6 COORDINATING CENTER RESPONSIBILITIES

The roles and responsibilities of Coordinating Centers vary by project. Sometimes a separate Data Coordinating Center is established for management of the research data, if data management is not a specific responsibility of the Coordinating Center. The need for IRB approval for work conducted by the Central or Data Coordinating Centers is based on where identifiable data are reviewed and managed.

The general responsibilities of a Coordinating Center are as follows, subject to applicable law, NIH policy and NIH delegation of authority.

- A. Development of documents, systems and standard operating procedures, as needed, for implementation of the protocol at each collaborating institution, which may include:
 1. Protocol and consent documents, including amendments.
 2. Case report forms.

3. Establishment of a data management system unless the PI or sponsor has designated another entity for this responsibility. This system includes storing and/or managing data, and, if the Center is also the data coordinating center, data analysis (See 20.C.6.N.)

B. Selecting appropriately qualified study sites and Principal Investigators

1. Ensuring, if the study is federally funded, that each collaborating institution holds an applicable OHRP-approved Federalwide Assurance (FWA).
2. Collecting and maintaining critical documents from affiliated investigators, e.g. resume/*curriculum vitae*, medical license (if required), certification of completion of training, laboratory certifications and laboratory reference ranges, signed COI disclosure forms.
3. Preparing any necessary agreements between sites and other entities to facilitate the research.

C. Ascertaining the protocol is reviewed and approved by the IRB at the collaborating institution or that there is a reliance agreement upon a central IRB prior to enrollment of subjects at that site.

1. Maintaining documentation of all affiliated sites IRB approvals for the protocol.
2. Assuring that affiliated sites are using the correct version of the protocol and consent document.
3. Assuring that IRB correspondence (continuing review and amendments) and study status changes are communicated to all affiliated sites or IRBs.

D. Data and safety monitoring.

1. Tracking, reporting and maintaining documentation of all unanticipated problems and disseminating the information to affiliated sites.
2. Support of an appropriate monitoring committee such as a Data and Safety Monitoring Board (DSMB) or Safety Monitoring Committee

- (SMC) if the research is an interventional study that is more than minimal risk, or if required by the protocol or Institute.
3. Oversee a Medical Monitor if required by law, protocol or Institute.
- E. Providing study-specific training to the research personnel at the affiliated sites.
1. Complete initial site training and monitoring before opening to enrollment.
 2. Notify sites when enrollment can begin.
 3. Provide additional site training, if needed, as the study progresses.
- F. Performing monitoring at external sites on a periodic basis to assess research study progress and compliance with the IRB-approved protocol. The Coordinating Center will establish a monitoring plan to be executed at all sites, including a plan for regular site visits to review consistency of local data entry (via case report forms, electronic data entry) based on source documents (documented physical exams and test result entries, radiologic studies etc.) to monitor data accuracy.
- G. Protecting the confidentiality of data transmission: Obtain a Certificate of Confidentiality if needed (see SOP 18-Privacy and Confidentiality).
- H. Coordinating randomization as applicable.
- I. Collecting subject registration from the sites and tracking subject enrollment.
- J. Ensuring informed consent is obtained and documented from each subject in compliance with federal regulations.
- K. Establishing an Executive Committee, as needed, which acts to:
1. Provide periodic updates to affiliated investigators on subject enrollment, general study progress, and relevant scientific advances.
 2. Hold Study Group meetings (such as gathering of PI's and coordinators from all sites) and other regular committee meetings.

3. Set policies and establish Standard Operating Procedures and Manuals of Operations.
 4. Establish secure websites for distribution of information, CRFs, FAQs, key document libraries and online training as necessary.
- L. Documenting receipt, shipment and storage of study specimens, drugs and/or devices.
1. Prepare agreements with core laboratories and pharmacies for centralized shipping and receiving.
 2. Establish Standard Operating Procedures and Manuals of Operations.
- M. Determine the need for a publication authoring committee, and if necessary establish the committee.
- N. If data are managed by a separate Data Coordinating Center or Statistical Center, those responsibilities are generally the following:
1. Designing and developing data forms.
 2. Providing instruction on use of the forms.
 3. Storing and/or managing data, data analysis, quality control and data and safety monitoring.
 4. Overseeing data transmission.
 5. Protecting confidentiality of data.

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.