GUIDELINE FOR COORDINATING CENTER STUDIES

Federal guidelines direct the Research Subjects Review Board (RSRB) to review 'coordinating center' activities (i.e., administrative processes and oversight responsibility) when the University of Rochester (UR) is coordinating multi-center collaborative research. The guidance below provides information for:

- Developing protocols to include the roles and responsibilities of parties involved in coordinating center studies;
- Overseeing and conducting coordinating center activities; and
- Preparing for initial and ongoing RSRB review of coordinating center protocols.

With the Single IRB requirement for federally-funded multi-site studies (NIH-funded as of January 2018 and all federally-funded beginning in January 2020), the function of the Coordinating Center will need to encompass the oversight for a single IRB for review and approval of research, rather than dealing with each individual enrolling site's IRB. And in some cases the Single IRB (or Reviewing IRB) may be the RSRB. When the RSRB is the Reviewing IRB, refer to Policy 504 IRB Reliance and Collaborative Research and the associated guidelines to help navigate that process.

Note: The Single IRB requirement does not apply to international studies, therefore when international enrolling sites are used, they will use their local IRB for review and approval.

Definitions:

Coordinating Center – an individual or group of individuals responsible for oversight and management of the conduct of a multi-center study at all collaborating intuitions. A coordinating center may be designated by the study sponsor or by mutual agreement among participating sites.

Lead Principal Investigator (PI) – the individual with primary responsibility for oversight and management of the conduct of the study at all participating research sites.

Site PI – the individual at each site who agreed to participle in the multi-center study and is responsible for the oversight of the conduct of the study at his or her center.

Protocol Documents – materials including the study protocol (see section on The Coordinating Center Protocol), operations manual (if applicable), model consent form(s), recruitment material, and any other documents pertinent for IRB review and approval.

Research Events – an incident, experience, or outcome that occurs during the conduct of a research study that may require reporting to the IRB, Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), and/or the Sponsor.

Responsibilities of a Coordinating Center

The design of a coordinating center study may range from a minimal risk, observational study conducted at a small number of institutions to a phase III, greater than minimal risk study conducted at a large number of institutions internationally. Likewise, the role of the coordinating center may range from overseeing the entire conduct of the study (e.g., protocol development, project management, data management) to responsibility for only limited portions of study oversight (e.g., collection and storage of study data only). Therefore, depending on the nature of the study and the coordinating center's role in the project, some oversight responsibilities addressed in this guidance may not apply. There may also be additional reporting and monitoring considerations required by the Food and Drug Administration (FDA), the study sponsor and/or international regulations that are not addressed here. Contact your IRB Coordinator for additional information as needed.

Generally, the responsibilities of a coordinating center include working with the lead PI to complete the following:

1. Responsibilities Prior to Study Initiation
    - Develop and refine the protocol documents.
    - Obtain approval of protocol documents, including model consent form(s), prior to distribution to the enrolling sites.
    - Oversee the development and design of data collection methods, e.g., case report forms.
    - Establish a method for data collection, maintenance and analysis.
    - Establish subcontracts with enrolling sites, contract research organizations, central laboratories, imaging service providers, and others as appropriate.
    - Assess enrolling sites to verify the site PI and study staff, as appropriate, are qualified in education, training and experience to conduct the study and to ensure the site has adequate resources (e.g., time, staff, space, etc.) to carry out study procedures.
    - Develop data and safety monitoring plan to ensure the safety of study subjects
    - Develop a method for supplying, handling and accounting for investigational products (drugs/devices/biologics).
    - Establish a plan to monitor the conduct of the study.
    - Document each enrolling site has a Federalwide Assurance (FWA) with the Office for Human Research Protections (OHRP).
    - Ensure each enrolling site obtains IRB approval and has an executed sub-contract prior to the initiation of subject enrollment.
    - Collect all required regulatory documents (see section on Essential Study Documentation below).
    - Provide enrolling site staff training on all aspects of study conduct, as applicable.

The FederalWide Assurance:

A FederalWide Assurance (FWA) is an agreement between an institution and the U.S. Department of Health and Human Services (DHHS) Office of Human Research Protection (OHRP). The assurance is the institution's written confirmation to the federal government that it will comply with regulations and principles pertaining to the ethical treatment of human research subjects. Without this assurance, an institution cannot conduct federally-funded research. If the terms are not honored, *all* federally-funded research at an institution can be shut down by the government.

When the University of Rochester is acting as a coordinating center, the study team must ensure that all participating sites have a current FWA, or equivalent per sponsor requirements for non-federally funded research. A copy of the University's most recent FWA can be found on the Office for Human Subject Protection's homepage.

2. Responsibilities During the Conduct of the Study

- Ensure all approved, amended protocol documents are distributed to enrolling sites and receive IRB approval prior to initiation of the changes.
- Maintain a regulatory file for the coordinating center, as well as, for each enrolling site (see section on Essential Study Documentation below).
- Monitor subject enrollment and participation.
- Ensure informed consent is obtained from each subject and consent is in compliance with federal, state and local regulations, as well as, the study protocol.
- Ensure compliance with the study protocol and data validity and integrity.
- Ensure timely reporting of research events to the enrolling site's IRB of Record, the study sponsor, and the Food and Drug Administration as needed. Depending on the nature of the event, the coordinating center may also need to determine whether any corrective or preventative action plan is required and whether all enrolling sites need to be notified of the event.
- Convey study-related information to enrolling sites, sponsors, and study-specific committees, as needed.
- Respond to enrolling site protocol inquires and questions.
- Provide enrolling site staff continued training on the conduct of the study, as necessary.

3. Responsibilities at the Time of Study Completion

- Ensure all enrolling sites are notified when, a) enrollment is complete, and b) all study-related activities are complete.
- Verify each enrolling site closes the study with their IRB.
- Ensure the data set and any stored samples are appropriately de-identified or coded and managed per the study protocol.

For additional information regarding the responsibilities of coordinating centers, please refer to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.

Note that coordinating center responsibilities are identified in this guidance document as "Sponsor" responsibilities).

The Coordinating Center Protocol

The protocol must address how the lead PI and coordinating center will assume responsibility for the overall conduct and management of the study, including the responsibilities listed above. This information should be included within the main study protocol, but may be provided as a separate addendum. In developing the protocol, consider the following:

- What is the organizational structure of the coordinating center? Are there separate committees responsible for administrative duties, protocol development, site monitoring, safety monitoring, data analysis, etc.? Will any responsibilities be delegated to other institutions or agencies (e.g., data management or specimen storage)? If so, the responsibilities allocated to separate committees and/or entities must be clearly identified.

- What training will be provided to enrolling site staff? Will there be study meetings, teleconferences or training sessions required for staff at enrolling sites prior to protocol implementation and throughout the course of the study?

- How will the coordinating center manage and/or monitor each site's study conduct including enrollment, research events, withdrawals and protocol deviations? How will sites report this information to the coordinating center? Will monitoring visits be conducted? If so, how often? What will the site monitoring visits entail?

- If investigational products (drugs/devices/biologics) will be used, how will they be provided to each enrolling site? How will dispensing will be monitored? What investigational product accountability procedures will be implemented?

- What are the procedures for study closures and early site terminations?

Monitoring Coordinating Center Studies

The purpose of monitoring is to:

- Ensure the rights and welfare of human subjects are protected;
- Ensure the study is conducted in compliance with the approved study protocol, federal regulations and sponsor requirements; and
- Ensure data validity and integrity.

Federal regulations (21 CFR Part 312 Subpart D and 812 Subpart C) require that studies conducted with an Investigational New Drug (IND) application or Investigational Device Exemption (IDE) be monitored by the sponsor. Studies not conducted under an IND or IDE should implement a monitoring plan that is appropriate to the nature and risk level of the study to ensure best practice in research, and may reference those regulations as guidance.

Per FDA guidance, the plan should address methods for monitoring the study, procedures for reviewing data and reporting research events, approaches for managing non-compliance and

methods for communicating monitoring activities. The nature and extent of a monitoring plan should be based on the needs of the study. Typically, monitoring plans for large scale, greater than minimal risk studies include a combination of in-person visits to enrolling sites (prior to the start of the study, periodically throughout the course of the study and at study closure) and remote evaluations throughout the conduct of the study. Smaller scale studies may monitor in the same manner, though to a lesser extent based on the study needs.

In developing the monitoring plan, consider the study objectives, study design, endpoints, risks related to the intervention, sample size and complexity of the study population. The primary focus of the monitoring plan should be on preventing and mitigating risks and errors related to the elements of the protocol that are most crucial for achieving the study objectives. These elements may include:

- Verifying informed consent was obtained prior to initiation of study procedures using a current, IRB-approved consent document
- Assessing protocol compliance, including adherence to study eligibility requirements, enrollment rates and investigational product accountability
- Determining whether any/all research events have been reported appropriately
- Reviewing data collection tools (i.e., case report forms) for completeness, consistency and accuracy, including source verifying the data provided
- Assessing whether the enrolling site is maintaining all essential study documentation (see below)

Documentation of monitoring should be maintained by the coordinating center (e.g., a monitoring report) and include the following at minimum: the date of monitoring activities; a summary of the monitoring activities conducted; descriptions of any noncompliance, data integrity or other discrepancies identified during monitoring; and a description of any actions taken to address the aforementioned issues.

Templates for tracking adverse events, protocol deviations, communications and training at enrolling sites are provided in the OHSP Study Documentation Tool Box. Use of these templates (aside from the "Site Regulatory Document Tracking Spreadsheet" described below) is not required by the RSRB; rather, they are provided as a resource for developing and carrying out the monitoring plan. The information that is required for initial and continuing review is discussed below under Ongoing RSRB Review of Coordinating Center Studies.

For additional information regarding monitoring, please refer to the FDA's Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines (Sections 5 and 8).

Essential Study Documentation

Coordinating centers are responsible for maintaining essential documentation for the coordinating center, as well as all enrolling sites. Essential documents are those that permit the conduct of the study and demonstrate compliance with the protocol and regulatory requirements. These documents include, but are not limited to:

- Dated IRB approval notifications for all coordinating center and enrolling site protocols, informed consent forms, recruitment materials and case report forms (including initial approvals, amendments and progress reports)
- Dated regulatory/ancillary committee approvals, authorizations and notifications
- Approved versions of all protocols, informed consent forms, recruitment material and case report forms
- Signed clinical trial agreements between all involved parties
- Evidence of investigator(s) qualifications, e.g., a signed/dated curriculum vitae
- Investigational product label samples, handing instructions, shipping records and accountability records
- All versions of the Investigator's Brochure, if applicable
- Monitoring visit reports
- Reportable research events (e.g., serious adverse event, unanticipated problem involving risk to subjects or others)
- Relevant communications between the coordinating center and participating sites

A complete list of essential documents can be found in Section 8 of the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.

RSRB Review of Coordinating Center Studies

As per the Single IRB requirement, there may be times when the RSRB can defer review of the Coordinating Center to the identified single IRB. When that is the case, the Coordinating Center will follow the Guideline and Flow Chart When University of Rochester Relies on a Non-UR IRB.

When the RSRB is the Reviewing IRB for the coordinating center, the RSRB will confirm that the protocol identifies adequate methods for addressing the following, as appropriate:

- Process to confirm that each enrolling site has an active FWA with OHRP;
- Distribution of protocol documents to enrolling sites and ensuring all sites have the most current version(s) of these documents;
- Documentation of the review and approval of enrolling site's initial IRB approval prior to the enrollment of subjects, as well as, all amendments and re-approvals;
- Collection and management of data from each site;
- Data and safety monitoring including the review of research events and protocol deviations from all sites;
- Training site study personnel.

When the RSRB is the Reviewing IRB for the Coordinating Center and the participating sites (psites), the Coordinating Center will submit the initial application with all protocol materials and the model consent documents. The RSRB will typically review the study by the convened board, regardless of the review level. Then psites will be added consistent with the Overview of the Multi-Site sIRB Submission Process in the Click IRB Manual for Study Staff. Refer to the Guideline and Flow Charts When University of Rochester is the Reviewing IRB for further information and processes.

Note: When the University of Rochester is both the Coordinating Center and an enrolling site and the RSRB is the Reviewing IRB for the study, the enrolling site personnel must be listed on the main study with the Coordinating Center study personnel. In this instance the model consent will be listed under Study-Related Documents, and the UR enrolling site consent form will be listed under the Local Site Documents.

- Continuing Review and Modifications should be submitted for approval like any other study, and will be reviewed consistent with the appropriate review level. At the time of continuing review, enrollment numbers are reported through each psite.
- Reportable research events should be reported according to Policy 801 Reporting Research Events and RSRB Guideline for Reporting Research Events.

When the RSRB is the Reviewing IRB for the Coordinating Center **only**, the Coordinating Center will submit the initial application with all protocol materials and the model consent documents. The RSRB will typically review the study through the expedited procedure. The Coordinating Center will provide documentation (typically a spreadsheet) that demonstrates enrolling site IRB submissions and approvals will be tracked. This document should provide a tentative (or final, if possible) list of enrolling sites and identify fields for the following items at each enrolling site, applicable: site name, site number, principal investigator, assurance number (FWA) and expiration date, and IRB approval & expiration dates (see the "Site Regulatory Document Tracking Spreadsheet" template provided in Appendix 1 as an example). The identification of enrolling sites, allows the RSRB the ability to contact representatives of those site IRBs, as necessary to ensure the protection of human subjects.

- Modification to the protocol, model informed consent form or other study documents must be submitted to the RSRB for review and approval prior to distribution to Reviewing IRB or the enrolling sites. It is recommended that amendments be numbered sequentially and identified by version dates to ensure proper document tracking. As with the initial review of the study, the RSRB will typically conduct an expedited review of amendments; however, depending on the nature of the modification and risk involved, full board review may be required. In certain circumstances, administrative changes (e.g., adding enrolling sites, modifying enrolling site information on recruitment materials, updating contact information, minor editorial changes to model consent documents) may be made without RSRB approval, but these changes should be submitted with the next formal amendment. Prior to making these changes, please verify with your RSRB Specialist whether formal review and approval of the change is required.
- Continuing Review – at the time of continuing review a current Site Regulatory Document Tracking Spreadsheet should be submitted in addition to the required elements of continuing review (e.g. enrollment numbers, data and safety monitoring reports).
- Research events that occurred at non-UR sites that were reported to the Reviewing IRB should be reported in real time to the RSRB for acknowledgement using the Report of New Information in the Click IRB review system. Note, however, that it is the responsibility of the Reviewing IRB for the non-UR site to make review determinations for the event occurring at the respective site (e.g., determination of an unanticipated problem involving risk to subjects or others). The real-time reporting of events, allows the RSRB to communicate with the enrolling site IRB, as necessary, to ensure the protection of human subjects.

Closing Coordinating Center Studies - Research study involving a coordinating center is considered complete when: all subjects have completed all study interventions; all protocol-defined analyses have been completed; post-study results have been communicated with subjects (if applicable); and all enrolling sites have closed the study with the Reviewing IRB.

To close a coordinating center application with the RSRB, submit a final continuing review and under Research Milestones check the first 4 boxes. Note that the Site Regulatory Document Tracking Spreadsheet should identify the IRB closure date of all enrolling sites.

APPENDIX 1: Sample Coordinating Center Worksheet Templates

NOTE: The following templates are provided for reference only and should be modified according to the needs of the study. Additional study documentation resources are available in the OHSP Study Documentation Toolbox.

Appendix 1.A: Site Regulatory Document Tracking Spreadsheet

Site #	Site Name	Site PI	Site Coordinator	FWA #	FWA Expiration Date	Initial IRB Approval Date	IRB Expiration Date	Amend 1 IRB Approval Date	Amend 2 IRB Approval Date	IRB Re-Approval Date

Appendix 1.B: Site Initiation Checklist Template

SITE INFORMATION					
Site Name:					
Site Principal Investigator:					
Site Number:					
IRB FWA Number:		**FWA Expiration Date:**			
SITE PERSONNEL					
Name	**Role**	**Required Documentation on File?**			
		CV	**License**	**HSPP**	**Financial Disclosure**
		☐	☐	☐	☐
		☐	☐	☐	☐
		☐	☐	☐	☐
		☐	☐	☐	☐
		☐	☐	☐	☐
		☐	☐	☐	☐
		☐	☐	☐	☐
Additional Comments:					

REGULATORY DOCUMENTS			
Have the following been obtained/completed?	**YES**	**NO**	**Additional Comments:**
Site Contract/Agreement	☐	☐	
Final Signed Study Protocol	☐	☐	
Site Specific FDA Form 1572	☐	☐	
Federal Certificate of Confidentiality	☐	☐	
Additional Comments:			

SITE TRAINING		
Date of Training:	**Training Method:**	☐ On-Site ☐ Teleconference ☐ Other (specify):
Training Completed By:		

Where the following items reviewed?	**YES**	**NO**	**Additional Comments:**
Background and Purpose	☐	☐	
Study Procedures			
Eligibility Criteria	☐	☐	
Registration and Randomization Procedures	☐	☐	
Informed Consent Procedures	☐	☐	
Drug Administration & Accountability	☐	☐	
Study Visits	☐	☐	
Procedures for Specimen Collection	☐	☐	
Adverse Event Reporting Procedures	☐	☐	
Treatment Discontinuation & Study Withdrawal Procedures	☐	☐	
Data Collection & Submission			
CRF Completion	☐	☐	
EDC Training	☐	☐	
Source Documentation	☐	☐	
Regulatory Binder Maintenance	☐	☐	
Site Monitoring Visits	☐	☐	
Additional Comments:			