

Yale University Human Research Protection Program

Investigator-Initiated and Multicenter Research HRPP Policy 120*

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Overview

This guidance discusses the responsibilities of a “coordinating investigator” and “sponsor-investigator”, management of clinical trials, considerations for Institutional Review Board review. Sponsor-investigators have additional federal regulatory requirements; whereas the responsibilities described for coordinating investigators are not federal requirements, rather they are recommendations to consider when tasked with this responsibility. Coordinating investigators must review the responsibilities of sponsor-investigators and determine which requirements must be implemented to increase subject protection and adherence to Good Clinical Practice.

Scope

This guidance is provided for principal investigators who will be engaged in human subject research as the lead site with at least one external institution.

Definitions

Central IRB: For multicenter studies, it is the IRB that conducts reviews on behalf of all study sites that agree to participate in the centralized review process.

Clinical trial/study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product, and/or to identify any adverse reactions to an investigational product, and/or absorption, distribution, metabolism, and excretion of an investigational product with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous [GCP E6 1.12].

Coordinating Investigator: A principal investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter study [Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (GCP E6) 1.19]. The responsibilities of the coordinating investigator(s) vary depending upon the requirements of the study.

Coordinating site, lead site, or coordinating center: The institution, department or center that agrees to be responsible for the conduct, administrative, or coordinating functions of a multicenter research project.

External Institution: An institution engaged in human subject research or a clinical investigation and does not meet the definition of faculty or staff at Yale University or Yale New Haven Hospital.

Human subject: The individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information [45 CFR 46.102(f)].

Investigator: A person responsible for the conduct of research at a site. If research is conducted by a team of individuals at a research site, the investigator is the responsible leader of the team and may be called the **principal investigator** [GCP E6 1.34].

Multicenter research/study: Human subject research conducted according to a single protocol but at more than one site, and therefore, carried out by more than one principal investigator.

Research: OHRP Definition of Research (from 46.102 (d)) “A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted

or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.”

FDA Definition of Research (from 21 CFR 50.3(c)) “Any experiment that involves a test article and one or more human subjects that is either subject to requirements for prior submission to the Food and Drug Administration under section 505(i), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted to, or held for inspection by the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provision of 21 CFR 58, regarding nonclinical laboratory studies.”

Sponsor: The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization that takes responsibility for and initiates a clinical investigation. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator [21 CFR 312.3(b)].

Sponsor-Investigator: An individual (usually the study Principal Investigator) who both initiates and conducts a clinical investigation, and under whose immediate direction the investigational product is administered or dispensed. The term does not include any person other than an individual investigator. The requirements applicable to a sponsor-investigator under FDA subpart [21 CFR 312 Subpart D] mean that sponsor investigators must follow the regulations for both an investigator and a sponsor [21 CFR 312.3(b)].

Planning the Conduct of Multicenter Research

Developing a plan in advance of managing or coordinating an investigator-initiated multicenter study should be done to enhance the ethical performance of the research study, ensure the appropriate conduct, and to promote the accuracy and quality of research data collected. The coordinating/sponsor-investigator should have the necessary resources (i.e. experienced staff, project manager, research coordinator(s), biostatistician, equipment, software, time, space, study monitors, Data Safety Monitoring Board, etc.) to adhere to the responsibilities agreed upon.

Responsibilities

General Responsibilities of Coordinating Investigators in Research Studies

A **coordinating investigator** is responsible for the overall coordination of research that involves investigators at different sites. Examples of the types of research that a coordinating investigator may oversee include (but are not limited to):

- research that involves minimal risk (i.e. collection of blood, biological specimens via noninvasive means, acquisition/banking/sharing/storage of specimens with collection of clinical data, survey studies)
- collection of data via non-invasive means **routinely employed in clinical practice** (i.e. MRI, ECG, etc.)
- prevention trials,
- quality of life trials, and
- research that does not involve the use or administration of Food and Drug Administration regulated investigational products (i.e. neither an investigational new drug application (IND) nor investigational device exemption (IDE) is required).

A coordinating investigator may be designated either by a sponsor or by mutual agreement of the participating centers. The general responsibilities of coordinating investigators may include:

General Responsibilities of Sponsors-Investigators in Clinical Trials

A **sponsor-investigator** is responsible for the conduct, initiation, management, and/or financing of a clinical trial. In investigator-initiated clinical trials the term “sponsor” is sometimes loosely used to solely describe the funding source instead of the associated responsibilities; therefore, the allocation of duties and functions should be defined and established prior to initiating the study [GCP E6 5.7] to ensure clarity of responsibilities. If something is delegated and is agreed upon, this should be documented. Any duty or function that is not otherwise delegated remains the responsibility of the sponsor [GCP E6 5.2.3].

Examples of the types of clinical trials that a sponsor- investigator may oversee include those that involve testing investigational products, drugs, biologics, and devices in human subjects, such as:

- [Phase I trials](#) - experiment in a small group of people (i.e. 20-80 people) for the first time to evaluate the investigational product's safety, determine a safe dosage range, and identify its side effects.
- [Phase II trials](#) - experiment in a larger group of people (i.e. 100-300 people) to see if the investigational product is effective and to further evaluate its safety.
- [Phase III trials](#) – experiment in large groups of people (i.e. 1,000-3,000 people) to confirm the investigational product's effectiveness, monitor side effects, compare it to commonly used treatments/devices, and collect information that will allow the investigational product to be used safely.
- [Phase IV trials](#), post-marketing studies to delineate additional information including the investigational product's risks, benefits, and optimal use. Phase IV trials are conducted after FDA approval.

In addition to the responsibilities listed above, the sponsor-investigator has additional regulatory responsibilities.

These responsibilities include (but are not limited to):

- selecting qualified investigators,
- ensuring adequate resources are available,
- ensuring that the investigation is conducted according to the signed investigator statement (FDA Form 1572), the investigational plan, protocol and applicable regulations,
- ensuring proper monitoring of the investigation,
- maintaining an effective Investigational New Drug (IND) application with respect to the investigations or submitting an IDE application to Food and Drug Administration (FDA),
- ensuring that the reviewing IRB(s) and FDA are promptly informed of significant new information or significant new adverse effects/risks,
- control and representation (labeling or marketing) of investigational product,
- ensuring that informed consent has been obtained for each human subject (unless exception requirements are met), and
- public registration of study with ClinicalTrials.gov.

Note: Documentation of the above must be maintained.

Management of Multicenter Clinical Trials (Sponsor-Investigators)

The ideas for management of multicenter research are specifically meant for clinical trials; however, please consider these as recommendations for best practice for certain multicenter research studies. In order to provide appropriate coordination at NSLIJHS and all participating external sites, the sponsor-investigator or designee should develop a financial plan, ensure adequate site selection, train sites involved, manage and provide oversight, ensure study-start-up and continuing review are appropriate.

1. Financial Plan

Research may be funded in many ways, including but not limited to (1) grants from government agencies and foundations (2) contracts with industry partners and (3) charitable donations.

2. Site Selection

Selecting qualified investigators and providing them with the information and resources they need to conduct the investigation properly is an important responsibility of a sponsor-investigator.

The sponsor-investigator must ensure that the project is conducted with adequate resources to follow the study protocol including but not limited to time, personnel, equipment, and space.

- Documentation of this may be obtained by surveying the site during the site-selection process and/or by having sites complete a Site Selection Survey which specifically asks about pertinent

resources needed.

When selecting sites, the Principal Investigator should review that the site has an adequate consent process, such as obtaining informed consent of each human subject prior to procedures (unless exception requirements are met).

- Documentation of this may be obtained by surveying the site during the site-selection process and/or by having sites complete a Site Selection Survey which specifically asks about their consent process.

Other selection criteria could include site experience, history of efficient study-start-up, strong subject recruitment and retention, history of robust compliance with regulations (lack of significant findings from agencies/inspectors).

- Documentation of site qualification may be obtained by collecting completed signed FDA Form 1572's, site's IRB assurance/membership, local lab certificates and ranges, lab director's Curriculum Vitae (CV).
- Qualifications of personnel based on training, education or experience may be obtained by collecting CVs and licenses (as applicable) for personnel at the different sites, and by having sites complete financial disclosure forms and a Site Selection Survey on pertinent research experience.

Note: CV's, Licenses and lab certificates should be current. The sponsor-investigator will need to track expiration dates and obtain current CVs, licenses and lab certificates throughout the study as applicable.

Protecting the rights, safety, and welfare of subjects must be done throughout the study.

- In order to increase the likelihood of this, the sponsor-investigator should ensure that all investigators and key study personnel have completed applicable human subjects training/education. Since institutions may have different requirements, general documentation for this may be obtained by requesting the human subjects training certificates or by having sites complete a Site Selection Survey which specifically asks about this for each investigator.

3. Study Start-up and Continuing Review

In addition to the above suggestions, ensuring that the investigation is conducted according to the applicable regulations should include:

- Obtaining executed agreement, contract and/or budget from each site.
- Obtaining documentation of site's initial IRB approval of the study as well as its subsequent renewals; and
- Ensuring all sites have the most current version of the protocol, investigational product information such as investigator's brochure (if applicable), consent form(s) and other study documents.

4. Training of Sites

The investigation must be conducted according to the signed investigator statement, the investigational plan, and applicable regulations. Doing the following may facilitate this effort:

- a. Ensure all key study personnel and study staff are trained on the conduct of the protocol and study procedures. Overall training and communication is usually accomplished through:

- Investigator's meetings and related training materials
 - Site Initiation Visits
 - Regularly scheduled telephone conference calls or meetings
 - Newsletters with relevant updates, tips, findings, recruitment progress, etc.
- b. Ensure sites have completed and signed a "Delegation of Responsibility" to document that all persons involved are aware of their research-related duties and functions.
- c. Communicate important announcements with all sites. Documentation of communication with sites which includes telephone conversations/conferences, emails, faxes, and mail should be maintained. Communication of important information can also include:
- Meeting minutes
 - Notification of safety reports or concerns
 - Study-related email broadcasts

What should training include?

The IRB/HRPP policies of each institution should be followed. The PI may require additional training based on the discipline of the research and other considerations such as the funding agency's requirements.

Should an Investigator's Meeting be conducted?

Yes. The investigation must be conducted according to the signed investigator statement, the investigational plan, and applicable regulations. This training may be given at a study start up meeting, a meeting held by webinar or some other technology. Documentation of attendance, agenda and participant questions must be maintained.

The meeting should include a formal presentation of the science behind the study and discuss relevant data. Review of the protocol should follow. If the study involves procedures that need to be conducted in a specific way, then have the relevant people present on how each assessment must be conducted. The review of the protocol should be followed by a review of data capture as it relates CRFs, reporting of unanticipated problems and query resolution. Lastly, a review of ICH Good Clinical Practice E6, investigator's responsibilities and applicable Federal regulations.

5. Study Management

Proper monitoring and oversight of the investigation should be detailed; topics to address this may include:

- central review of data and statistical analysis;
- review safety data via Data Safety Monitoring Board/Committee or Data Safety Monitoring Plan;
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- providing a process for specimen collection, analysis and tracking; and
- obtaining current site-specific Screening and Enrollment, reports or logs.
- Ensure the integrity of the data, including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data
- The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

6. Investigational Products

Control of the products (drugs or devices) under investigation must be done by having a process to order, ship, store, dispense, and account for the investigational product at all participating sites. Investigational product's accountability may include:

- Documentation that site has process in place for proper receipt and storage of the investigational product.
- Documentation of process/management of manufacturer issues related to investigational product (i.e. defects, returns, etc.).
- The following must be maintained at the coordinating center if functioning as a central dispensing entity or at each individual site if decentralized:
 - investigational product request forms and orders/prescriptions,
 - dispensation and/or shipping records and inventory,
 - return shipment documentation, and
 - disposition records.

7. Quality Management

The sponsor should implement a system to manage quality throughout all stages of the trial process. Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols, tools, and procedures for data collection and processing, as well as the collection of information that is essential to decision making. The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent. The quality management system should use a risk-based approach as described below.

- Critical Process and Data Identification: During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and reliability of trial results.
- Risk Identification: The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (standard operating procedures, personnel, etc.) and clinical trial level (trial design, data collection informed consent process, etc.).
- Risk Evaluation: The sponsor should evaluate the identified risks, against existing risk controls by considering the likelihood of errors occurring, the extent to which such errors would be detectable, and the impact of such errors on human subject protection and reliability of trial results.
- Risk Control: The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures. Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.
- Risk Communication: The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.
- Risk Review: The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.
- Risk Reporting: The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report.

8. Handling of Unexpected Events or Unanticipated Problems

A plan to manage issues from participating sites should also be developed in advance. For example, the plan should address how the following will be handled:

- concerns of non-compliance,
- unanticipated problems involving risks to subjects or others,
- interim results requiring changes to the research study or early study termination,
- site termination due to non-compliance or violation of contract/protocol, and
- receipt and evaluation of deviations and protocol exceptions.
- If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

IRB Review for Multicenter Research/Clinical Trials

Institutions involved in multi-institutional research may utilize joint IRB review, reliance upon the review of another qualified IRB, or similar arrangements [21CFR56.114]. These arrangements are made to decrease unnecessary duplication of effort, delays, and increased expenses in the conduct of multicenter research. In general, an institution is considered engaged in human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research¹. A centralized Institutional Review Board (IRB) review process may be used, with execution of appropriate IRB agreements, to ensure that the multicenter human subject research has appropriate IRB oversight. Each involved institution/IRB needs to determine if central IRB review is appropriate given the local context, and the IRB of record will need to ensure that the criteria for IRB approval are met [21 CFR 56.111, 45 CFR 46.111].

Plan for:

- Obtaining and distributing the investigational product (if applicable) as well as establishing a method for maintenance and accountability. If there is a controlled substance proposed for use, assure that each investigative site PI has appropriate Federal and State DEA licensure
- Review and appropriate disseminate unanticipated problems involving risk to subjects or others, protocol violations, changes to the study, interim results, protocol modifications;
- review of each site's local IRB approval documents and consent forms (if applicable);
- documentation of initial and continuing IRB review*;
- confirming that each participating site has a Federalwide Assurance on file with the Office of Human Research Protection;
- Establishing a method for assuring that all sites have the most current version of the protocol;
- collection and management of data from all sites; and
- processing, reporting and evaluating unanticipated problems, protocol violations, deviations, and serious adverse events from participating sites.
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*Each participating site is responsible for adhering to their local/reviewing IRB policies.

Data Monitoring

The fundamental reason to establish a data and safety monitoring committee and/or plan is to enhance subject safety and data credibility. In order for a study to be IRB approved, the research plan must make adequate provisions for monitoring the data collected to ensure the safety of subjects

[21CFR56.111(s)(6)]. The IRB will review the plan to ensure that it is appropriate for the anticipated risk to subjects and complexity involved. The following can serve as a guide for detailing your plan and also help the IRB determine if it is adequate to protect research subjects²:

- State whom will be responsible for data and safety monitoring, such as an individual investigator, the sponsor, or a Data and Safety Monitoring Board (DSMB).
- Describe the number of people who will be responsible for this task and their qualifications to function in this capacity.
- Describe the planned frequency of data analysis. Will data be analyzed on a per time basis (e.g. every 6 months), or on a per-subject basis (e.g. after 10 subjects), or in response to specific events (e.g. after any fatality)? How frequently will a report be submitted to the IRB? This may assist the IRB in determining if the frequency of review is appropriate for the type of study and the potential risks involved.
- Describe the study stopping rules regarding the potential outcomes of the study that are likely to have a major impact on the rights or welfare of research participants.
- If there is a potential for conflicts of interest (financial or otherwise) that might bias the data-monitoring process, state how you will manage or eliminate it.
- State in a general way what will be reviewed.
- Define the process or procedure for implementing the recommendations for the continuation or conclusion of the study.
- Define their authority.

What is a DSMB?

A DSMB is a group of individuals with pertinent expertise that regularly reviews accumulated data from one or more ongoing clinical trials to ensure the safety of participants in the trials and the validity and integrity of the scientific data generated. It is also known as a Data and Safety Monitoring Committee. It is usually composed of three to six experts in at least two areas: 1) medical issues (the disease, drug, device, procedure, or outcome measures) and methods issues (clinical trials design, data management, and statistical analysis)². Since individuals closely involved with the study may not be objectively review the data and concerns that arise, it is recommended that the members be independent of the study.

A DSMB in investigator-initiated studies that involve:

- Interventional research at multiple centers, and/or
- High risk studies with investigational agents or devices
- Or when required by regulation [21 CFR 50.24] or sponsor (i.e. National Institutes of Health, Department of Veterans Affairs).

Depending on the type of study and potential risks involved, the NSLIJ IRB may not require a DSMB and instead require a data safety monitoring plan (DSMP) to oversee data and subject safety. While FDA regulations require monitoring for all clinical trials, its current regulations do not require the use of formal committees to do so. The FDA regulations specifically require a Data Monitoring Committee for research in emergency settings in which the informed consent requirement is waived. Therefore, it is highly recommended to discuss the study with the IRB or sponsor during the planning phase to ascertain their requirements especially when not required by regulations.

For guidance on the establishment and operations of a Clinical Trial Monitoring Committee, refer to the FDA's "Guidance for Clinical Trial Sponsors: Establishment and Operations of a Clinical Trial Monitoring Committee, March 2006."

Sometimes additional sites are added after the initiation of the study to enhance recruitment or increase diversity of the subject population, for example. If this is the case, the protocol should address how the sites & data will be incorporated.

Compliance not only emphasizes the need for adequate study-wide communication, but also documenting it. If it is not documented, then it didn't happen. In addition, address problems that appear to be systemic by implementing study-wide solutions.

References

¹Office for Human Research Protections, Department of Health and Human Services Guidance on Engagement of Institutions in Human Subjects Research; October 16, 2008

²Part of the bulleted information was obtained from "Institutional Review Board: Management and Function" by Elizabeth A. Blankert, Robert J. Amdur; 2nd Ed. 2006

³Fundamentals of Clinical Trials, 3rd ed. Lawrence M. Friedman, Curt D. Furberg, and David L. DeMets.

Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance: 1.19, 1.34, 1.40, 1.53, 1.54, 4.9.1, 5.2.3, and 5.7

21 Code of Federal Regulations: 56.111, 56.114, and 312.3(b)

45 Code of Federal Regulations: 46.111

Guidance for Clinical Trial Sponsors: Establishment and Operations of a Clinical Trial Monitoring Committee, March 2006

Guidance for Industry: E6(R2) Good Clinical Practice: Integrated Addendum to ICHE6(R1), March 2018.

Revision History

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*As of December 08, 2017, this policy has not yet been reviewed by the Office of General Counsel, Yale University