**Supervisory Responsibilities of Investigators**

**PURPOSE**

The purpose of this document is to provide guidance to investigators about supervisory responsibilities of investigators.

**GUIDANCE**

This document provides an overview of responsibilities of a person who conducts a research protocol involving a drug, biologic, medical device, radiotherapy, or use of surgery for invasive procedures. This also covers research involving behavioral science, survey or interview techniques.

The intent of this is to help investigators meet their responsibilities with respect to protecting human subjects and ensuring the integrity of the data for research protocols. The investigator must adhere to the procedures outlined in the protocol at all times.

This document does not encompass all of the responsibilities of the investigator. Instead, this document is intended to assist the investigator in making the determination to appropriately assign responsibilities related to the conduct of the research. This is intended to clarify the M. D. Anderson Institutional Review Board (IRB) expectations concerning the investigator’s responsibility: (1) to supervise a research protocol in which some protocol tasks are delegated to employees or colleagues of the investigator or other third parties, and (2) to protect the rights, safety, and welfare of protocol participants.

When an investigator conducts a clinical investigation, many of the investigator’s responsibilities are outlined in the Statement of Investigator Form 1572 (see Chapter 1.006 Clinical Research Forms Database for an example of a Statement of Investigator Form 1572). Form 1572 is an agreement between the investigator and the Food and Drug Administration (FDA) assuring that the clinical investigation will be conducted in compliance with all applicable regulations. The M. D. Anderson IRB does not require that this form be submitted for review. As most industry-sponsored protocols require the utilization of this form, investigators are encouraged to check with their sponsor for submission requirements. The IRB will prepare an official acknowledgement letter if required by the Sponsor. Additionally, M. D. Anderson does not require each physician that may potentially consent a participant to a protocol be listed on the Form 1572. Investigators are encouraged to check with their sponsor for other requirements that may apply.

Form 1572 requires that the investigator make the following commitments:

- To conduct the protocol(s) in accordance with the relevant, current protocol(s) and to only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects;
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- To personally conduct or supervise the described investigation(s);
- To inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met;
- To report to the sponsor adverse experiences that occur in the course of the investigations(s) in accordance with 21 CFR 312.64;
- That he/she has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug;
- To ensure that all associates, colleagues, and employees assisting in the conduct of the protocol(s) are informed about their obligations in meeting the above commitments;
- To maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available to FDA for inspection in accordance with 21 CFR 312.68;
- That an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation;
- To promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others;
- To not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects;
- To comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR 312.

There are specific regulations governing the use of medical devices in research protocols. Investigator responsibilities in the conduct of these protocols are outlined in the FDA regulations at 21 CFR 812. Generally, the responsibilities of the investigator include:

- To conduct the investigation in accordance with 1) the signed agreement with the sponsor; 2) the investigational plan; 3) the regulations in 21 CFR part 812 and other applicable regulations; and 4) any conditions of approval imposed by the reviewing IRB or FDA.
- To supervise all testing of the device involving human subjects
- To ensure that the requirements for obtaining informed consent are met
- To permit an investigational device to be used only with subjects under the investigator's supervision and to supply an investigational device only to persons authorized to receive it
- To return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs upon completion or termination of a clinical investigation or the investigator's part of an investigation
- To maintain accurate, complete, and current records relating to the investigator's participation in an investigation:
  - All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports;
  - Records of receipt, use or disposition of a device;
  - Records of each subject's case history and exposure to the device;
  - The protocol, with documents showing the dates of and reasons for each deviation from the protocol, and
  - Any other records that FDA requires to be maintained by regulation or by specific
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- requirement for a category of investigations or a particular investigation.

- To permit FDA to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify participants

- To prepare and submit to the sponsor and, when required by regulation, the reviewing IRB and monitor, the following complete, accurate, and timely reports:
  - Any unanticipated adverse device effect occurring during an investigation
  - Progress reports on the investigation
  - Any deviation to the investigational plan made to protect the life or physical well-being of a subject in an emergency
  - Any use of the device without obtaining informed consent
  - A final report
  - Any further information requested by FDA or the IRB about any aspect of the investigation.

**Investigator Responsibilities Related to the Supervision of Research**

It is common practice for investigators to delegate certain protocol-related tasks to employees, colleagues or other third parties (individuals or entities not under the direct supervision of the investigator). When tasks are delegated by the investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated and the investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the research.

In assessing the adequacy of supervision by an investigator, the M. D. Anderson IRB focuses on four major issues: (1) whether delegated individuals were qualified to perform such tasks, (2) whether protocol staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the protocol, (3) whether there was adequate supervision and involvement in the ongoing conduct of the protocol, and (4) whether there was adequate supervision of oversight of any third parties involved in the conduct of a protocol to the extent such supervision or oversight was reasonably possible.

**A. What is Appropriate Delegation of Protocol-Related Tasks?**

The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience to perform the delegated task.

Appropriate delegation is primarily an issue for tasks that would be considered to be clinical or medical in nature, such as evaluating protocol participants to assess clinical response to an investigational therapy (e.g., global assessment scales, vital signs) or providing part of the medical care provided to participants during the course of the protocol. Most clinical/medical tasks require formal medical training and may also have licensing or certification requirements. Such licensing requirements will vary from state to state.

Clinical investigators should take such qualifications/licensing requirements into account when considering to whom it would be appropriate to delegate specific tasks.
The FDA has identified instances in which protocol tasks have been delegated to individuals lacking appropriate qualifications. Per the FDA, examples of inappropriate delegation include:

- Screening evaluations, including obtaining medical histories and assessment of inclusion/exclusion criteria, conducted by individuals with inadequate medical training (e.g., a medical assistant)
- Physical examinations performed by unqualified personnel
- Evaluation of adverse events by individuals lacking appropriate medical training, knowledge of the clinical protocol, and knowledge of the investigational product
- Assessments of primary protocol endpoints (e.g., tumor response, global assessment scales) by individuals lacking appropriate medical training and knowledge of the protocol
- Informed consent obtained by individuals who lack the medical training, knowledge of the clinical protocol, or familiarity of the investigational product needed to be able to discuss the risks and benefits of a clinical protocol with prospective participants

Some protocols specify the qualifications of the individuals who are to perform certain protocol-required tasks, and these protocols must be followed even if state law permits differently qualified people to perform the task.

For example, even if the state in which the protocol site is located permits nurse practitioners to perform physical examinations under the supervision of a physician, if the protocol specifies that physical examinations must be done by a physician, a physician must perform such exams.

The investigator should maintain a list of the appropriately qualified persons to whom significant protocol-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks, and identify the dates of involvement in the protocol. An investigator should maintain separate lists for each protocol conducted by the investigator.

**B. What is Adequate Training?**

The investigator should ensure that there is adequate training for all staff participating in the conduct of the protocol. The investigator should specifically anticipate the possibility of staff turnover during the conduct of the protocol (particularly if the protocol is of long duration) and plan to ensure that there is adequate training of any replacement staff. The investigator should ensure that staff:

- Have a general familiarity with the protocol
- Have a specific understanding of the details of the protocol and the investigational product, relevant to the tasks they will be performing
- Are aware of regulatory requirements and acceptable standards for the conduct of research protocols, both in respect to conduct of a clinical protocol and human subject protection
- Are competent to perform the tasks that they are delegated
- Are informed of any pertinent changes during the conduct of the protocol and
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- educated or given additional training as appropriate
- If the sponsor provides training materials for investigators in the conduct of the protocol, the investigator should ensure that staff receives the sponsor's training, or information from the training, that is pertinent to their role in the protocol.

C. What is Adequate Supervision of the Conduct of an Ongoing Research Protocol?

The investigator should have a detailed plan for the supervision and oversight of a protocol. Supervision and oversight should be provided even for individuals who are highly qualified and experienced. A plan might include the following elements, to the extent they apply to a particular protocol:

- Routine meetings with staff to review protocol progress and update staff on any changes to the protocol or other procedures
- Routine meetings with the sponsor's monitors
- A procedure for correcting problems identified by protocol personnel, on-site monitors or auditors, or other parties involved in the conduct of a protocol
- A procedure for documenting the performance of delegated tasks in a satisfactory manner and, where appropriate, verifying findings (e.g., observation of the performance of selected assessments or independent verification by repeating selected assessments)
- A procedure for ensuring that the consent process is being conducted in accordance with 21 CFR Part 50 and that protocol participants understand the nature of their participation, risks, etc.
- A procedure for ensuring that information in source documents is accurately captured on the Case Report Forms
- A procedure for dealing with data queries and discrepancies identified by the protocol monitor
- Procedures for ensuring protocol staff comply with the protocol, adverse event assessment and reporting, and other medical issues that arise during the course of the protocol.

The investigator should have sufficient time to properly conduct and supervise the protocol. The intensity of the supervision should be appropriate to the staff, the nature of the protocol, and the participant population. The following factors may compromise the ability of an individual investigator to provide adequate supervision of the conduct of an ongoing research protocol, and thus contribute to regulatory issues with the research:

- Inexperienced protocol staff
- Overburdened protocol staff
- Complex protocols (e.g., many observations, large amounts of data collected)
- Large number of participants enrolled at a site
- A patient population that is quite sick
- Conducting a large number of protocols concurrently
- Conducting a protocol from a remote (i.e., off-site) location;
- Conducting a protocol at multiple sites under the oversight of a single investigator, particularly where those sites are not near each other (e.g., sites that are geographically distant, in another city, county, state, or country). It is preferable for any site with substantial enrollment to have an identified investigator with clear responsibilities.
D. What are an Investigator’s Responsibilities for Oversight of Other Parties Involved in the Conduct of a Research Protocol?

1. Protocol staff not in the direct employ of the investigator

The staff involved directly in the conduct of a protocol may include individuals who are not in the direct employ of the investigator. The investigator should take steps to assure that staff, that are not directly employed, are qualified to perform delegated tasks and have received adequate training on carrying out the delegated tasks and on the nature of the protocol. The investigator is responsible for supervision of the protocol tasks performed by this staff, and this responsibility exists, no matter how qualified and experienced these staff members are. In the event that the staffs’ performance of protocol-related tasks is not adequate and cannot be made satisfactory by the investigator, the investigator should document the observed deficiencies in writing to the staffs supervisor(s). Depending on the severity of the deficiencies, the protocol may need to be voluntarily suspended until personnel can be replaced.

2. Parties other than Protocol Staff

There are often critical aspects of a protocol performed by parties not involved directly with the research and not under the direct control of the investigator.

For example, clinical chemistry testing, radiologic assessments, and electrocardiograms are commonly done by a central independent laboratory or an outside facility hired by the sponsor. Under these arrangements, the central laboratory usually provides the test results directly to the sponsor, who then relays the results to the investigator. In this case, the sponsor has retained the services of the laboratory or the outside facility and thus, is responsible for seeing that these parties are fulfilling their responsibilities for the protocol.

Less frequently, a protocol may require that investigators arrange to obtain information critical to the protocol that cannot be obtained at the investigator’s facility. For example, if the protocol requires testing with special equipment or expertise not available at the investigator’s facility, the investigator might make arrangements for someone outside the facility to perform the test. In this case, the results are provided directly to the investigator, who then submits the information to the sponsor.

Procedures are particularly important when assessments are crucial to the evaluation of the efficacy or safety of an intervention or to the decision to exclude participants who would be exposed to unreasonable risk. Where such assessments are retained by the investigator, the investigator should take steps to ensure that the facility is adequate (e.g., has the required certifications or licenses). The investigator may also institute procedures to ensure the integrity of data and records obtained from the party providing the information (e.g., a process to ensure that records identified as coming from the party are authentic).

Investigators should carefully review the reports from these external sources for
results that are inconsistent with clinical presentation. To the extent feasible, and considering the specifics of protocol design, the investigator should evaluate whether results appear reasonable, individually and in aggregate.

If an investigator detects possible errors or suspects that results from a central laboratory might be questionable, the investigator should contact the sponsor immediately, and report the incident to the IRB.

E. Protecting the Rights, Safety and Welfare of Protocol Participants

Investigators are responsible for protecting the rights, safety, and welfare of participants under their care during a protocol. The investigator should provide a reasonable standard of medical care for protocol participants for medical problems arising during participation in the protocol that are, or could be related, to the protocol intervention. The investigator should be readily available to provide such care during the protocol or should assure that other identified, qualified individual(s) are available to provide such care. Failure to adhere to the protocol can expose participants to unreasonable risks.

1. Reasonable Medical Care Necessitated by Participation in a Research Protocol

During and following a participant's participation in a protocol, the investigator should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the protocol. The investigator should inform a participant when medical care is needed for intercurrent illness(es). The investigator should inform the participant's primary physician about the participant's participation in the protocol. The participant must agree to their primary physician being informed.

If the investigator does not possess the necessary skills to provide adequate medical care for the participant, the investigator should make every effort to obtain appropriate care. For example, if a carotid stent is placed in a participant by an interventional neuroradiologist and the participant suffers a cerebral stroke, the neuroradiologist should assess the clinical status of the participant and transfer the participant to a neurology service. Participants should receive appropriate medical evaluation and treatment until resolution of any condition related to the protocol intervention that develops during the course of their participation in a protocol, even if the follow-up period extends beyond the end of the protocol at the investigative site.

2. Reasonable Access to Medical Care

To protect participants from unnecessary risks, investigators should be available to participants during the conduct of the protocol at their site. Availability is particularly important where participants are receiving a drug that has significant toxicity or abuse potential. For example, if a study drug has potentially fatal toxicity, the investigator should be readily available by phone or other electronic
communication, and in reasonably close proximity to protocol participants (e.g., not in another state or on prolonged travel). Protocol participants should be clearly educated on the possible need for such contact and on precisely how to obtain it, generally by providing pertinent phone numbers or websites in writing. Prior to undertaking the conduct of a protocol, prospective investigators should consider whether they can be available to the extent needed given the nature of the protocol.

If the investigator is not going to be available for some period during the study, responsibility for protocol participants should be delegated to a specific qualified physician who will be readily available to participants. This delegation should be documented in a 1572 or investigator agreement and also submitted to the IRB for review (as a change in the research activity requiring IRB review under 21 CFR 56.108(a)).

3. Protocol Violations that Present Unreasonable Risks

There are occasions when a failure to adhere to the protocol may be considered a failure to protect the rights, safety, and welfare of participants. For example, failure to adhere to inclusion/exclusion criteria that are specifically intended to exclude participants for whom the study drug or device poses reasonable risks (e.g., enrolling a participant with decreased renal function in a protocol in which decreased function is exclusionary because the drug may be nephrotoxic) may be considered failure to protect the rights, safety, and welfare of the enrolled participant. Similarly, failure to perform safety assessments intended to detect drug toxicity within protocol-specified time frames (e.g., CBC for an oncology therapy that causes neutropenia) may be considered failure to protect the rights, safety, and welfare of the enrolled participant. Investigators should seek to minimize such risks by adhering closely to the protocol.