

Subinvestigators

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The principal investigator (PI) in a clinical study is responsible for proper conduct of the study at a research site. Principal investigators may delegate certain responsibilities to other site personnel. Some of these responsibilities may only be delegated to individuals designated as "subinvestigators." The FDA requires that subinvestigators be identified on Form 1572¹ so it can identify the key players on the study. As we will see below, "subinvestigator" is a misleading term; as far as the FDA is concerned, the role encompasses study personnel who "perform critical trial-related procedures and/or...make important trial-related decisions." The FDA does not say so explicitly, but it is clearly more concerned about sins of omission than sins of commission in designating subinvestigators.

There are three types of subinvestigators. The first type is a "junior investigator." This type of subinvestigator may serve as the PI's second in command, or have responsibility for a subset of subjects, e.g., at a satellite site, but under the PI's supervision. If the satellite site is located down the hall, supervision by the PI is straightforward. However, if the satellite is orbiting around Jupiter, the subinvestigator is probably a PI, or should not be conducting the study at all.

The second type of subinvestigator is a "specialist investigator" who performs technical tasks, such as medical procedures, tests and assessments that require special expertise, especially when there is the potential for significant impact on the health status of the subjects. FDA guidance cited below gives examples of tasks that require someone to be designated as a subinvestigator, albeit not in a manner that clearly divides the shades of gray. The PI may or may not have the same expertise. If not, the presence of the subinvestigator completes the set of qualifications that the study needs to conduct the study. For example, an internist may be qualified to be a PI on a pain study, provided a neurologist is a subinvestigator. A study coordinator who "performs critical trial-related procedures" but does not otherwise fit anyone but the FDA's idea of an investigator fits awkwardly into this category.

The third type of subinvestigator is a "backup investigator." This type of investigator fills in when the PI is unavailable, e.g., busy with clinical patients or attending an investigators meeting. Most studies should have at least one such subinvestigator as a backup to the principal investigator. However, subinvestigators cannot solve the mystery of the phantom PI; every study needs a proper leader.

Physicians who refer subjects to the study may qualify as subinvestigators if they conduct screening histories and physical exams or perform study procedures, such as endoscopies. Some PIs designate referring physicians as subinvestigators for honorary or motivational purposes.

Subinvestigators are sometimes called "co-investigators," but the concepts are different. While a subinvestigator's role is subsidiary to that of the PI, a co-investigator is a co-PI, with his or her own FDA Form 1572.

Regulations, Guidelines and Guidances

In June 1996, the International Conference on Harmonisation published "ICH Guideline for Good Clinical Practice E6(R1)." ² This guideline defines a subinvestigator as:

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). [1.56]

The guideline further clarifies that subinvestigators can fill in for the PI's gaps in expertise:

A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions. [4.3.1]

In July 2008, the FDA published "Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions - Statement of Investigator (Form FDA 1572)." ³ This draft guidance answers several questions about subinvestigators:

Who should be listed as a subinvestigator in Block #6? FDA's regulation at 21 CFR 3 12.3(b) states: "In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 'Subinvestigator' includes any other individual member of that team." 21 CFR 3 12.53(c)(1)(viii) requires the investigator to provide "A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s)."

The purpose of Block #6 is to capture information about individuals who, as part of an investigative team, will be assisting the investigator and who make a direct and significant contribution to the data. The decision to list an individual in Block #6 depends on a higher level of responsibility (i.e., whether he/she is performing significant study-related duties). In general, if an individual is directly involved in the treatment or evaluation of research subjects, that person should be listed on the 1572. For example, as part of the protocol of a clinical investigation, if each subject needs to visit a specified internist, who will perform a full physical to qualify subjects for the study, that internist should be listed in Block #6. [VII.30]

Should...research coordinators be listed in Block #6? If a research coordinator is performing critical study functions and collecting and evaluating study data, the coordinator should be listed in Block #6. If the research coordinator is only transcribing data and maintaining study files, the coordinator does not need to be listed. [VII.32]

Must the investigator be a physician? The regulations do not require that the investigator be a physician. Sponsors are required to select only investigators qualified by training and experience as appropriate experts to investigate the drug (21 CFR 3 12.53(a)). In the event the clinical investigator is a non-physician, a qualified physician (or dentist, when appropriate) should be listed as a subinvestigator for the trial and should be responsible for all trial-related medical (or dental) decisions. [I.4]

Should co-investigators be listed on the 1572 in Block #1? Is it acceptable to have two investigators? Co-investigators should not be listed in Block #1. The term co-investigator is not defined in FDA regulations. As commonly used, the term is meant to indicate that each co-investigator is fully responsible for fulfilling all of the obligations of an investigator as identified in 21 CFR 3 12.60. Thus, under 21 CFR 3 12.3(b), each co-investigator is an investigator, and, as such, must sign a separate 1572. It is acceptable to have more than one investigator at a particular site. This is distinct from a subinvestigator (see #30), whose role in the study is more limited. [II.19]

Do individuals who are listed in Block #6 on the 1572 have to submit information about their financial interests? Yes. Under 21 CFR Part 54 (Disclosure of Financial Interests by Clinical Investigators), a person listed or identified as an investigator or subinvestigator and who is directly involved in the treatment or evaluation of research subjects must submit financial disclosure information to the sponsor. For purposes of this financial disclosure regulation, the term "investigator" also includes the spouse and each dependent child of the investigator and subinvestigator. (21 CFR 54.2(d) and 54.4). [VII.34]

In March 2001, the FDA published "Guidance for Industry: Financial Disclosure by Clinical Investigators."⁴ This guidance clarifies the definition of a subinvestigator in the financial disclosure context:

What does FDA mean by the definition of clinical investigator and subinvestigator? Is it necessary to collect financial information on spouses and dependent children of subinvestigators? The definition of "clinical investigator" in Part 54 is intended to identify the individuals who should be considered investigators for purposes of reporting under the rule, generally, the people taking responsibility for the study at a given study site. For drugs, biological products and devices, it should be noted that hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care but who do not make direct and significant contribution to the data, are not meant to be included under the definition of clinical investigator. For purposes of this financial disclosure regulation, the term "investigator" also includes the spouse and each dependent child of the investigator and subinvestigator. [IV.12]

In May 2007, the FDA published "Guidance for Industry: Protecting the Rights, Safety, and Welfare of Study Subjects - Supervisory Responsibilities of Investigators." This draft guidance discusses which responsibilities principal investigators can delegate to other study personnel.⁵ The following three passages are especially relevant to subinvestigators:

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 clinical or medical in nature, such as evaluating study subjects to assess clinical response to an investigational therapy (e.g., global assessment scales, vital signs) or providing part of the medical care provided to subjects during the course of the study. Most clinical/medical tasks require formal medical training and may also have licensing or certification requirements. [III.A.1]

Subinvestigators should report directly to the investigator (i.e., the clinical investigator should have clear responsibility for evaluating the individual's performance and should have the authority to hire/fire the subinvestigator). [III.A.3]

If the investigator is not going to be available for some period during the study, clinical responsibility for study subjects should be delegated to a specific qualified physician who will be readily available to subjects. This delegation should be documented in a 1572 or investigator agreement (where the physician should be listed as a subinvestigator) and also submitted to the IRB for review (as a change in the research activity requiring IRB review under 21 CFR 56.108(a)). [III.B.2]

Subinvestigator Responsibilities

The responsibilities of a subinvestigator depend on his or her role in a study. A technical specialist may have very limited responsibilities, e.g., just performing a medical procedure.

Other subinvestigators may have broad responsibilities, much like those of the PI. These responsibilities must be documented, along with relevant qualifications. The PI may take personal responsibility for some aspects of the study, e.g., handling serious adverse events. If a subinvestigator is inexperienced or unproven, the PI may closely monitor his or her work, e.g., by sitting in on some informed consent discussions and reviewing visit documentation.

Subinvestigator responsibilities must include the following:

- Sign the study's financial disclosure form.
- Provide a current signed CV or statement of education and experience annually.
- Participate in the study only to the extent qualified.
- Perform study activities as required by the protocol and applicable regulations.
- Protect the rights, safety and welfare of subjects as the primary consideration.

Subinvestigator responsibilities may include, but may not be limited to, the following:

- Read and understand the informed consent form, protocol, and investigator's brochure.
- Ensure that study responsibilities are delegated to qualified personnel only and that delegation is properly documented.
- Assess subject compliance with use of the study drug and follow-up visits.
- Assess subject response to therapy.
- Evaluate subjects for adverse events.
- Ensure that medical care is provided (or at least made available) to subjects for any treatable adverse event.
- Ensure that subject recruitment is conducted ethically and efficiently.
- Ensure that the study is conducted in accordance with applicable regulations, guidelines and standard operating procedures (SOPs).
- Obtain or ensure that proper written informed consent is obtained from each subject prior to participation in the study.
- Ensure that study drugs and devices are used for protocol purposes only.
- Ensure that investigational drugs and devices are stored in a secure facility.
- Ensure that only concomitant therapy authorized by the protocol is used.
- Ensure that study events are recorded in the subject's source documents.
- Ensure that serious and unexpected adverse events are reported promptly to the PI or study coordinator.
- Ensure that complete and accurate source documentation is maintained for each study subject, recording all required or pertinent observations and data during the subject's participation in the study.
- Be available (or properly delegate responsibility to another qualified medical professional) to see subjects, answer their questions, and resolve medical issues during study visits.
- Be accessible (or properly delegate responsibility to another qualified medical professional) between study visits to answer subjects' questions and resolve medical issues during study visits.
- Sign and ensure that the study documentation for each study visit is completed.
- Learn how to properly conduct studies in accordance with government regulations, guidelines, GCP and SOPs.

Subinvestigator Selection

The PI must determine whether potential subinvestigators can fulfill the above requirements and meet the following additional criteria:

- Motivation and time to participate in the study
- Necessary qualifications (training, licenses and experience) to carry out his or her responsibilities
- Access to a suitable facility, including equipment, exam rooms, and storage facilities for study documents, test articles, and biological specimens
- Other required resources, such as qualified personnel to assist him or her in the study
- Not currently listed in the FDA's list "Investigators Ineligible to Receive Investigational New Drugs"

Conclusion

FDA Form 1572: Statement of Investigator requires that PIs commit to "personally conduct or supervise the described investigation(s)." Without subinvestigators, it would be very difficult for many qualified investigators to conduct clinical research. The 1572 form further requires PIs to provide documentation of "education, training and experience that qualify the investigator as an expert in the clinical investigation of the drug for the use under investigation." The role of subinvestigator enables inexperienced investigators to gain such expertise.

References

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