From: OC GCP Questions
To: [redacted]
Subject: RE: Sub-Investigator responsibilities
Date: Tuesday, September 23, 2014 4:02:00 PM

Dear [Redacted]-

Thank you for your question. The investigator (also referred to as the principal investigator or PI) is responsible for supervising the conduct of the clinical investigation and to protect the rights, safety, and welfare of participants in drug and medical device clinical trials. PI's commit themselves to personally conduct or supervise the investigation. It is common practice for investigators to delegate certain study-related tasks to employees, colleagues, or other third parties, but the investigator remains responsible for providing adequate supervision of those to whom tasks are delegated. Essentially, the PI may delegate tasks on a given study, but they may not delegate their role or responsibilities as PI.

FDA's regulations found in 21 CFR 312 subpart D (see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.4) outline the responsibilities of sponsors and investigators for FDA-regulated studies conducted under an Investigational New Drug Application (IND). FDA's regulations found in 21 CFR 320 (see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=320) outline requirements for FDA-regulated bioavailability and bioequivalence studies.

FDA's definition of investigator is found at 21 CFR 312.3:

> Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). 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.

FDA has a guidance document for industry titled, "*Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects*" that can be found at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm187772.pdf. This guidance was developed to clarify for investigators and sponsors FDA's expectations concerning the investigator's responsibility (1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties and (2) to protect the rights, safety, and welfare of study subjects.

Section III.A.3. of this guidance says:

> *3. What Is Adequate Supervision of the Conduct of an Ongoing Clinical Trial?*
>
> For each study site, there should be a distinct individual identified as an investigator who has supervisory responsibility for the site. Where there is a subinvestigator at a site, that individual should report directly to the investigator for the site (i.e., the investigator should have clear responsibility for evaluating the subinvestigator's performance and the authority to terminate the subinvestigator's involvement with the study) and the subinvestigator should not be delegated the primary supervisory responsibility for the site.

Section III.B.2 further states:

> *2. Reasonable Access to Medical Care*
>
> Investigators should be available to subjects during the conduct of the trial for medical care related to participation in the study. Availability is particularly important when subjects 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 24 hours a day and in reasonably close proximity to study subjects (e.g., not in another state or on prolonged travel). Study subjects should be clearly educated on the possible need for such contact and on precisely how to obtain it, generally by providing pertinent phone numbers, e-mail addresses, and other contact information, in writing. Prior to undertaking the conduct of a study, prospective investigators should consider whether they can be available to the extent needed given the nature of the trial.
>
> During any period of unavailability, the investigator should delegate responsibility for medical care of study subjects to a specific qualified physician who will be readily available to subjects during that time (in the manner a physician would delegate responsibility for care in clinical practice). If the investigator is a non-physician, the investigator should make adequate provision for any necessary medical care that the investigator is not qualified to provide.

As this guidance implies, FDA recognizes that there may be times when an investigator may be unavailable, but in those circumstances, the investigator should delegate responsibility for medical care of study subjects to a specific qualified physician who will be readily available to subjects during that time.

Based on the information provided in the regulations and guidance, it would not be appropriate for the PI to routinely or wholly delegate the task of delegation to a subinvestigator on any given study. Keep in mind that the investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

The ICH GCP E6 Good Clinical Practice: Consolidated Guidance, (which is recognized as official FDA guidance – see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf) also includes definitions for investigator and subinvestigator:

> **1.34** Investigator: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.
>
> **1.56** Subinvestigator: 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). See also Investigator.

Again, the expectation is that the investigator is the person responsible for the conduct of the clinical trial at a trial site and that this person is the responsible leader of the team.

The FDA regulations at 21 CFR 312.50 require sponsors to select qualified investigators. If a proposed PI at your study site is not able to adequately fulfill the responsibilities of an investigator, then that person should not assume the role of PI. You may want to designate another qualified individual who meets the qualifications and expectations for this crucial role; someone who can be actively involved in and supervise the proposed study. The sponsors that you work with may also have concerns if your PI's are not able to fulfill the role of investigator for their studies so I recommend you discuss this issue with them as well. I would also imagine that the IRB(s) you are working with likely have expectations of PIs, so I also recommend you talk to them as well.

I hope this information is useful. If you need further information and/or have additional questions, please feel free to contact us at the official GCP mailbox, gcp.questions@fda.hhs.gov. You may also find it useful to access the set of redacted GCP e-mails found at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriestoFDAonGoodClinicalPractice/default.htm since we find that many questions and concerns are repeated over time.

Best Regards,

Janet

Janet Donnelly, RAC, CIP
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Office of Special Medical Programs, Food and Drug Administration

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From: [Redacted]
Sent: Thursday, September 18, 2014 11:13 AM
To: OC GCP Questions
Subject: Sub-Investigator responsibilities

GCP Questions office:

I am the [Redacted] at [Redacted]. We are a [Redacted] and we conduct both Bio-equivalence and phase 2 to 3 studies on site. I have question regarding delegation of clinical trial roles:

For each trial we have ongoing, we have a Principal Investigator (PI). Each PI then acts as a Sub-Investigator for other ongoing

studies to provide appropriate coverage. As per GCP regulations, PI delegates to the Sub-I for specific trial related activities. Due to travel/illness/vacation, the PI may not be at site to delegate specific trial related tasks to qualified study staff. We would like to explore the possibility of allowing appropriately qualified Sub-I (or Co-I) to delegate study tasks to other qualified study personal. The question is, can the PI "delegate the task of delegation' to the Sub-I, who would then sign off the delegation of other qualified personal on studies?

I would appreciate your feedback in this respect.

Best regards,

[Redacted]