From: OC GCP Questions
To: [redacted]
Subject: RE: Sub-Investigator responsibilities
Date: Wednesday, October 22, 2014 12:02:00 PM

Dear [Redacted]-

Thank you for your email. I didn't see any specific questions, however, I think that you might be asking whether you can develop an SOP that predefines tasks considered to be clinical or medical in nature, that must routinely be carried out either by the PI or an individual qualified by education, training, experience and licensure where relevant (e.g., subinvestigator) AND predefine other study tasks that are not considered to be clinical or medical in nature that can routinely be delegated and carried out by other appropriately trained individuals (e.g., clinical research coordinators, phlebotomists).

I previously shared with you the FDA's regulations regarding the responsibilities of sponsors and investigators for FDA-regulated studies conducted under an IND. These regulations do not specifically address the delegation of study tasks. When the regulations are silent, sponsors, CROs, investigators, IRBs and institutions are free to develop their own procedures and practices as long as applicable regulatory requirements are met.

I'm glad that you were able to review the FDA's guidance I previously shared with you. FDA is not able to review or comment on your SOPs as it is your responsibility to prepare adequate SOPs. However, I hope the information I provided is helpful to you as you develop your SOPs.

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) includes some information on delegation at section 4.1.5:

> 4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

Section 5.18.4 of this guidance, Monitor's Responsibilities also says:

> 5.18.4 Monitor's Responsibilities
>
> The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:
>
> (h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

We are aware that delegation of study tasks is typically done on a study-by-study basis as each study may have unique study requirements that require careful consideration by the PI in determining what, if any tasks can be delegated, and to whom. I recommend that even if you have an SOP that outlines delegation responsibilities that you ensure there is a mechanism by which the PI carefully considers each study and the unique aspects of the tasks required by each study.

I am a little confused by your comment that you will "define the tasks that **require** PI delegation". There is no regulatory requirement for PI's to delegate any study tasks. It is critical to remember that the PI is responsible for supervising the conduct of the clinical investigation and protecting the rights, safety, and welfare of participants in FDA-regulated studies. While the PI may delegate some tasks on a given study, they may not delegate their role or responsibilities as PI. The PI is also accountable for any regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

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
Policy Analyst, Office of Good Clinical Practice
Office of Special Medical Programs, Food and Drug Administration

---

From: [Redacted]
Sent: Monday, October 20, 2014 11:41 AM
To: OC GCP Questions
Subject: RE: Sub-Investigator responsibilities

Dear Janet.

Thank you for the response. As we are developing the delegation SOP's, I have read the Guidance for Industry "Investigator Responsibilities- October 2009" I have a few additional questions:

We are a [Redacted] and we have staff trained to perform specific tasks for the studies that we perform. We are in the process of reviewing the tasks that are delegated and we would like to define the tasks that require PI delegation vs. tasks that can be routinely performed by appropriately trained individuals without the need to delegate for each study

The guidance (Page 3) states that delegation is "an issue for tasks considered to be clinical or medical in nature". To that end, we would like to define the tasks that would need to be delegated, we have the following tasks that we are proposing to be routinely mandate for PI's to perform themselves or to delegate to appropriately trained individuals:

- Obtaining Informed Consent
- Physical examinations
- Evaluation/judgement of Adverse Events or SAE's
- Evaluating subject eligibility based on Inclusion/Exclusion criteria
- Assessment of Primary Endpoints such as skin irritation scores etc.
- Evaluation/judgement of Lab results
- Drug dispensation
- IMP administration

For other study related tasks we would like to allow appropriately trained individuals (Clinical Research Coordinators, phlebotomists etc.) to perform without the need for specific delegation for each study. These tasks would include:

- Obtain Height, weight, ECG's, spirometry. Vital signs (using a validated automated NIBP machine) – these tasks are performed by appropriately trained individuals
- eCRF data entry
- Phlebotomy for laboratory sample collection
- Performing Urine pregnancy & Drug testing – not evaluating the result
- Performing skin testing (e.g. allergy skin testing) – not evaluating the result

We would appreciate your input on these questions as we are trying to modify our SOP's to ensure that we are compliant with the regulations.

Best regards,

[Redacted]

From: OC GCP Questions [mailto:gcp.questions@fda.hhs.gov]
Sent: September-23-14 4:02 PM
To: [Redacted]
Subject: RE: Sub-Investigator responsibilities

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
Policy Analyst, Office of Good Clinical Practice
Office of Special Medical Programs, Food and Drug Administration

---

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]