From: OC GCP Questions
To: [redacted]
Subject: 1572/Coverage/Grading & Attributions
Date: Monday, September 18, 2017 9:24:00 AM
Attachments: [redacted]

Good morning –

I can answer your email in general.

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 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 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?

Good morning –

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 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 clinical 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.

I cannot specifically speak to toxicity evaluations/attributions as my office does not have the expertise to cover this topic. If your study is under IND you can always speak with the regulatory project manager of the IND for clarification. In general, anyone that is intimately involved in the clinical study should be listed on the 1572. If they are not listed on the 1572 or delegation log I don't think they can evaluate toxicity levels or AEs but they should report them to the CI and the study team for evaluation and follow-up for subject safety.

Please see FDA's guidance on the 1572 form. This guidance outlines individual roles in an IND clinical study.
https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

Additionally, if I have not fully answered the questions in your email you may contact the Center for Drugs (CDER) directly at druginfo@fda.hhs.gov

Kind regards,

Doreen M. Kezer, MSN
Senior Health Policy Analyst
Office of Good Clinical Practice
Office of the Commissioner, FDA

From: [redacted]
Sent: Friday, September 15, 2017 5:02 PM
To: OC GCP Questions
Subject: 1572/Coverage/Grading & Attributions

Good afternoon,

There are 3 inquiries I need to get some clarification on from you:

1) What is the current policy on infusion nurses (who are not the clinical research nurse) for a given patient documenting any toxicities/Adverse Events and being able to grade those items? The infusion nurses unlike the CRN's are not listed on the 1572 or Delegation of Authority Log.
2) What is the policy of an physician (covering over night or on the weekend) who is not listed on the 1572 being able to document toxicities/adverse events and grade those items?
3) In regards to attribution of toxicity to study drug – is this something that must be done prior to treatment, or can the attribution be done following treatment? Does only the PI have the responsibility to complete attribution or can a Sub-I also complete attribution?

[redacted]