From: OC GCP Questions
To: [redacted]
[redacted]
Subject: Trial-related medical decisions and care
Date: Tuesday, August 07, 2018 9:18:00 AM
Attachments: [redacted]

Good morning:

This office cannot specifically answer your questions as all clinical trials are different and sponsor and protocol requirements vary. I can offer you the following information.

The regulations are very broad. The regulations require that sponsors choose investigators qualified by training and experience (see 21 CFR 312.53(a)). The regulations also require that investigators commit themselves to personally conduct or supervise the investigation (see 21 CFR 312.53(c)(1)(vi)(c)).

Please see FDA's 1572 guidance document (link) here.
www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

4. 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 312.53(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. (ICH E6 section 4.3.1; www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf).

FDA's regulation at 21 CFR 312.3(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 312.53(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)."

However, who can substitute for the clinical investigator of record in performing study tasks depends upon many factors, including the specifications in the protocol and the qualifications of the person in question.

The protocol may specify only certain study staff may perform specific tasks. In addition, the country/state of the site may have specific requirements regarding who can do various medical tasks - e.g., conducting medical examinations. In most U.S. states most medical tasks require licensed medical personnel and, depending upon the state, that may only be a licensed medical doctor. Some states do allow licensed nurse practitioners or doctor's assistants to perform a limited number of such tasks. If the protocol allows and the person is qualified in the site's locale, then he/she should be listed in the study's delegation log as capable of covering specified tasks in the absence of the site's clinical investigator

Additionally, training, education, and experience required for sponsor personnel may necessarily, and appropriately, vary depending on the type of product, the indication, the study being conducted, and its associated risk. FDA's regulations are not explicit as to what constitutes adequate training, education and experience, nor do they outline specific qualifications, including whether such personnel must hold an active medical license. Moreover, sponsors have discretion in determining what qualifications are needed in certain positions based on the general recognition that this would include education, training and experience pertinent to the particular clinical study and its design and execution, as well as familiarity with human subject protection (HSP) regulations, recordkeeping, data integrity, and good clinical practice (GCP) standards and requirements. Whether or not certain sponsor personnel should hold an active medical license depends on the considerations outlined above.

Again, FDA would expect physicians and study staff to follow state and local laws regarding medical licensure and medical practice requirements in addition to sponsor requirements.

I hope this information is helpful. Please contact us again at gcp.questions@fda.hhs.gov should you have additional questions.

Kind regards,

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

This communication does not constitute a written advisory opinion under 21 CFR 10.85, but rather is an informal communication under 21 CFR 10.85(k) which represents the best judgment of the employee providing it. This information does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: [redacted]
Sent: Tuesday, August 07, 2018 3:20 AM
To: GCP.questions@fda.hhs.org
Subject: Trial-related medical decisions and care

Dear colleagues,

I ask you to please help to understand the FDA position on "medical decisions" definition.
The "Guidance for Industry Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects" requires the following: " In all cases, a qualified physician (or dentist) should be responsible for all trial-related medical (or dental) decisions and care", this corresponds to ICH GCP E6 p. 2.7.
In some US states law allows Physician Assistant (PA) perform subjects' exams, assessment of ECG, labs etc. and prescribe drugs independently of their supervising MD (MD is not required to see the patient during the visit). I work on the sponsor side and from my perspective delegating such tasks as diagnosis, decision of study drug administration/treatment continuation and assessment of AE is overdelegating which jeopardizes subjet's safety.

In light of above could you please suggest if the following approaches could be considered acceptable from FDA perspective?
1. The PA conducts the entire visit, including subject questioning, review of lab results, assessment of ECG, physical exam and takes decision on treatment continuation. The MD reviews notes in subject medical records a few days later (3-5) and signs them;
2. The PA assess if subject meets all inclusion and doesn't meet any exclusion criteria and randomizes subject. The MD reviews notes in subject medical records a few days later (3-5) and signs them;
3. Study coordinator (a nurse or medical technician) questions the subjects regarding adverse events and captures them in the medical records. The MD reviews these records retrospectively (when subject already left the site), assess AE causality and signs medical records. In this case my concern is, for example, in situation where nurse will capture "pain in left arm" the MD might suspect heart attack or where nurse captures a set of symptoms the MD will establish a diagnosis.

The conditions are: the Protocol doesn't specify the qualification needed to perform the above actions, but just repeats the Guidance general wording above; delegation by PI is documented appropriately; state law allows Physician Assistant perform exams, establish the diagnosis and prescribe drugs.

If possible, could FDA also provide the examples of "trial-related medical decisions" which always should be taken by MD/DO only?

Thank you very much in advance!

With kind regards,
[redacted]