From: OC GCP Questions
To: [redacted]
Subject: PI Oversight
Date: Monday, July 06, 2015 2:27:26 PM

Good afternoon –

Yes it is very difficult to specifically answer your questions. FDA 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)).

Since you state that there were minimal problems with compliance I am not sure what can be done about the situation other than to express your concerns with the sponsors of the studies the CI is overseeing.

It might be helpful for you to review FDA's guidance on Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects (available 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.

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,

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Office of Good Clinical Practice
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From: [redacted]
Sent: Sunday, July 05, 2015 11:25 AM
To: OC GCP Questions
Subject: PI Oversight

I recently monitored a university medical center in the [redacted] where a physician was the PI of multiple complex, open and active protocols. She also has a full time, very busy clinical practice. There is one sub-investigator on all of her studies who has little involvement, if any (other than coming to the required training) in the clinical trials. Her clinical practice is bursting at the seams with patients waiting for hours. She has no "protected time" specifically for her research. There are no formal meetings with the research staff. Discussions about the research patient status are generally done "whenever they can catch her in the hall between cases." I informed the site that I felt she had too many trials going on for a physician with an

excessively busy solo surgical practice and no designated research time.

Nevertheless, in my monitoring of the trials at her site, there is minimal problems with compliance. There are, however, some problems with delays in signing off on some documents such as AE reports. Still, she has a very good, dedicated staff to whom she has delegated these responsibilities.

My question is how many protocols is too many– particularly for a very busy clinician with no protected time for research. I know the FDA doesn't like to provide numbers and is keen on referring to the regulations. So I have proactively noted the regulations and GCP regarding investigator responsibilities for you with a summary at the bottom.

I know when FDA auditors come in, the first thing they ask for is a list of all the current trials that the PI is actively participating. Would it be a problem if the auditor saw that this full time, very busy clinician is currently conducting 35 complex corporate sponsored Phase Ib, II, and III interventional trials? Would it be a problem if it were 15 trials or 50 trials? What is too much and what is sufficient? I know this is difficult to answer.

Thank you in advance

Applicable regulations and GCP for Investigator Responsibilities:

In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. [21 CFR 312.3]. Per the FDA FORM 1572, he/she is responsible to:

- Personally conduct or supervise investigation.
- Follow protocol-only make changes after notifying the sponsor unless subject at risk.
- Ensure all persons assisting with the study are informed of obligations.
- Inform subjects that drugs are being used for investigational purposes.
- Ensure informed consent (21 CFR Part 50) an IRB review, approval and reporting (21 CFR Part 56)
- Report to sponsor adverse events (21 CFR 312.64)
- Maintain adequate and accurate records (21 CFR 312.62) and make them available for inspection in accordance with 21 CFR 312.68
- Ensure initial and continuing review by an IRB and report all changes to research and unanticipated problems involving risks to subjects, not make any changes without IRB approval except where necessary to eliminate immediate hazards
- Comply with other requirements in 21 CFR 312

GENERAL CLINICAL INVESTIGATOR RESPONSIBILITIES [21 CFR 312.60]

- Ensuring that an investigation is conducted according to the Signed investigator statement (Form 1572) (if applicable), Investigational plan, and Applicable regulations.
- Protecting the rights, safety, and welfare of subjects under the investigator's care
- Control of drugs under investigation
- Ensuring that informed consent is adequately obtained according to 21 CFR 50
- Ensuring IRB review, approval and reporting requirements are met per 21 CFR 56
- Control of investigational drug (312.61)
- Record keeping and retention (312.62) An investigator is responsible for: Maintaining adequate records of the disposition of the drug
- Accurate case histories that record all observations, and
- Other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation
- An investigator is required to maintain investigation records for:2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated
- 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication
- Investigator reports (312.64) Progress reports to sponsor
- Safety reports - Immediately report any adverse event that is alarming (e.g. an unexpected event that is serious or life-threatening)
- Safety reports - Record non-serious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol
- Final report to sponsor
- Financial disclosure to sponsor
- Promptly update as needed during the course of the investigation and for 1 year following study completion.

IN SUMMARY, THE RESPONSIBILITIES OF THE PI INCLUDE:

✓ Follow the current protocol

✓ Personally conduct or supervise investigation(s)

✓ Ensure that all persons assisting in conduct of studies are informed of their obligations

- ✓ Ensure informed consent (21 CFR 50) and IRB review, approval, and reporting (21 CFR 56) requirements are met
- ✓ Obtain the informed consent of each human subject to whom the drug is administered
- ✓ Notify the sponsor before making changes in the protocol
- ✓ Notify the IRB and obtain IRB approval before making changes in the protocol
- ✓ Report adverse events to the sponsor
- ✓ Maintain adequate and accurate records
- ✓ Make records available for inspection
- ✓ Comply with all other requirements in 21 CFR 312
- ✓ Report Financial Interests to the Sponsor