From: OC GCP Questions
To: [redacted]
Subject: Clarification about Safety Reporting requested from [Redacted] Laboratories
Date: Thursday, January 09, 2014 8:38:37 AM

Good morning –

The transfer of obligations to a contract research organization is located in FDA regulations under 313.52. (See below)
CFR - Code of Federal Regulations Title 21

21 CFR 312.52 states --

Transfer of obligations to a contract research organization. (a) A sponsor may transfer responsibility ***for any or all of the obligations set forth in this part to a contract research organization****. Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.*

(b) A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" in this part apply to a ***contract research organization to the extent that it assumes one or more obligations of the sponsor.***

What the transfer of obligations spelled out in 21 CFR 312.52 does is give the contracted party regulatory responsibilities for whatever they contract to do. This allows FDA to take regulatory action against the contracted party whenever inspectional findings at the contracted site evidence failure to comply with the pertinent regulations. That does not, however, completely relieve the sponsor of their regulatory responsibilities. FDA still holds the sponsor responsible for studies conducted under their auspices. Therefore, sponsors need to ensure that parties to whom they contract what the regulation delineate as their responsibilities comply with the regulations. While there are probably a number of ways to ensure this, the most common way is to audit the practices of the contracted party, both before issuing the contract and during the course of the study. Sponsors can contract out to a CRO some or all of their responsibilities - development of the protocol, selection of the clinical investigators, monitoring of the study, review of adverse events (commonly the purview of a medical monitor), data management, etc. If all responsibilities are contracted out than all documentation of the study files and procedures (including safety reporting) would be required of the CRO as the CRO can be inspected by FDA.

Additionally, contract research organizations are mentioned in the link below. This new FDA document release in March 2011 outlines what may happen should an FDA inspection occur of a CRO. You will find this document helpful.

http //www fda gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133770 pdf

CROs are also mentioned in ICH-E6 Guidance on Good Clinical Practice --in section 5.2, page 24. See the link below

http://www.fda gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

A discussion related to safety reporting for BA/BE studies occurs in FDA's draft guidance "Safety Reporting Requirements for NDs and BA/BE Studies" (available at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf). This draft guidance was issued in concert with FDA's final rule, which published on September 29, 2010, "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products." Information on this final rule is available at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226358 htm

If I have not adequately answered your questions, you may contact the Center for Drugs (CDER) directly at druginfo@fda.hhs gov or by phone 1-888-463-6332.

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

From: [Redacted]
Sent: Wednesday, January 08, 2014 12:55 PM
To: OC GCP Questions; OC GCP Questions
Cc: [Redacted]
Subject: Clarification about Safety Reporting requested from [Redacted] Laboratories

Dear Sir/Madam,

I would greatly appreciate if you could clarify a point for me with regard to the regulations below about Safety reporting for BA/BE studies:

Under 21 CFR 320 31(d)(3) – "The person conducting the study, including any contract research organization, must notify FDA and all participating investigators of any serious adverse event, as defined in 312.32(a), observing during the conduct of the study as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence .....The person conducting the study, including any contract research organization, must also notify FDA of any fatal or life-threatening adverse event from the study as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence".

As I understand it:

- Both Sponsor and CRO are responsible for Safety reporting of SAEs to the FDA.
- Sponsor and CRO don't each need to submit the 3500A, as the FDA only requires one report for a particular SAE
- Sponsor can contract the responsibility of submitting the 3500A to CRO, or the Sponsor may retain that responsibility and submit the reports themselves.
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Questions

- In a situation where the Sponsor has kept the reporting responsibilities, is the CRO obligated to also maintain documents for proof of submission ?
- In the event of an FDA audit for the CRO, must the CRO records mirror the Sponsor records in every respect, meaning 3500As, proof of submission with dates,

cover letters, and receipt etc.?

- What exactly would the CRO need to retain and show with respect to Safety reporting, in the event of an FDA audit ? What information is the Sponsor, if reporting, obligated to share with the CRO.
- Are rules similar for IND studies [21 CFR 312 32(c)(1)(v)] as well, vis-a-vis the CRO?
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Many thanks in advance for your help.

Best Regards,
[Redacted]