From: OC GCP Questions
To: [redacted]
Subject: Delegation of Safety / Determining Severity / Causality
Date: Thursday, October 22, 2015 12:03:00 PM

Dear [redacted],
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 regulations 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 FDA document release in March 2011 outlines what may happen should an FDA inspection occur of a CRO. You will find this document helpful. 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
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122 pdf
A discussion related to safety reporting for BA/BE studies occurs in FDA's guidance "Safety Reporting Requirements for INDs and BA/BE Studies" (available at www.fda.gov/downloads/Drugs/.. /Guidances/UCM227351.pdf). This 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: www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrug NDApplication/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, or the GCP mailbox at gcp.questions@fda hhs.gov.
I hope this information is helpful to you. If you need further assistance, please feel free to contact the GCP mailbox at gcp questions@fda.hhs.gov .

Best regards,

Sheila

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From: [redacted]
Sent: Wednesday, October 21, 2015 2:58 PM
To: OC GCP Questions
Subject: Delegation of Safety / Determining Severity / Causality

Good Afternoon,

Please see our question below:

"We have referenced the below regulation, and Guidance, and respectfully ask if a Sponsor can delegate determination of severity/causality reporting for safety to an ARO or CRO when the Sponsor holds the previous safety data?"

Regulation Sec. 312.52 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

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Safety Reporting Requirements for INDs and BA/BE Studies, December 2012
Under 21 CFR 312 32, the amended requirements revise the definitions used for safety reporting and make clear when to submit expedited safety reports The requirements distinguish circumstances in which it is appropriate to submit individual cases and circumstances in which **cases should be aggregated and compared to cases in a control group** and submitted only if the event occurs more frequently in the drug treatment group Compliance with these requirements will increase the likelihood that submitted information will be interpretable and will meaningfully contribute to the developing safety profile of the investigational drug and improve the overall quality of safety reporting In addition, reducing the number of uninformative individual reports will enhance the ability of sponsors, FDA, investigators, and IRBs to focus on safety issues that affect public health

[redacted]