From: OC GCP Questions
To: [redacted]
Subject: Question on CRF
Date: Wednesday, July 19, 2017 1:05:00 PM
Attachments: [redacted]

Good afternoon –

Sorry for the delay in responding. I needed to confer with a few of my OGCP colleagues. We understand that you are the CRO but we suggest you contact the sponsor of the study to determine what they want to correct the issues outlined in your emails. Also because the situation appears to be a bit confusing and note-to-file outlining the issues and the corrective actions would be appropriate. Once the AE CRFs are corrected, remediation and training for all staff should be instituted and documented. Lastly because my office does not specifically comment on issues that you have outlined, we suggest that if the study is under IND that you contact the regulatory project manager at FDA for advice and guidance as completing the AE CRF inaccurately could potentially affect the data already collected for the study.

Kind regards,

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

From: [redacted]
Sent: Thursday, July 13, 2017 8:42 AM
To: OC GCP Questions
Cc: [redacted]
Subject: Question on CRF

To whom it may concern,

I am writing as the [redacted] My office is listed as the CRO and sponsor representative for the PI on our trials. We manage phase I and II IST cancer trials and are a central coordinating office, overseeing the trials at our local member hospitals who implement the trials and treat the patients. My office's responsibilities are inclusive of the following: initial protocol concept writing, creation of CRFs and databases, data querying, review of data for deviations, reporting of SAEs, amendment creation, data repository, overall study maintenance and publication (this is a short list of all responsibilities).

I am writing to obtain confirmation on the best way to handle the following situation

pertaining to documentation of data on CRFs by our site. We are overseeing 3 trials using the same regimen of treatment. The regimen includes 4 drugs and 1 of those drugs is being provided by the manufacturer of the drug and they are also financially supporting 2 of the 3 trials. One drug is being combined with a standard treatment to create the regimen being tested. My office created the AE CRF and submitted this with all other CRFs to the site for data collection. One study opened earlier than the others, but all 3 are currently open. When the first trial opened, the AE CRF asked for the relationship "to study treatment" in one column and then provided another column to ask the sites to document relationship to anything else if applicable (i.e disease etc). When data began being submitted the research staff asked some questions about what we were capturing, as some were reporting this to be related to the one study drug being provided and others to the regimen. We updated the AE CRF to clarify and then had one column asking for the relationship specific to the one drug and we kept the other column asking for the site to document the relationship to anything else (i.e. the other drugs in the regimen, disease, a concomitant medication etc). When the other trials opened the AE CRF was in line with the latest change- meaning there was one column asking for the relationship in the context of the study drug and one column asking the site to document any other relationship (i.e. the other drugs in the regimen, disease, a concomitant medication etc).

On quality review, my office found that even though the AE CRF now specifically asked for the relationship to the study drug, some relationships being listed in that column (R, PR etc) were actually pertaining to the overall regimen and not the one drug. This led to an overall review of logs, to be sure my office correctly received and understood, so we can report, the relationships of the AEs.

To ensure completeness, we have queried each patient (we are doing one study at a time) to obtain confirmation from the site on how the relationship of the AEs were reported on the log. We sent 2 types of queries: 1) for the older AE logs which had a column asking for "relationship to study treatment," we asked them to confirm if relationships in this column referred to the drug or the regimen and 2) For the newer AE logs, which specifically noted the study drug in one column and which had an "other" column, we asked the site to confirm if relationships listed in the column were to the drug or regimen.

For the older AE logs, which noted "study treatment" : when the site replied to note the relationships were to the regimen overall, unless otherwise specifically noted, we felt this was acceptable.

However, for the newer logs, which defined the column as pertaining to the one study drug, when the site replied noting that the relationships were to the overall study regimen and not specific to that drug, unless otherwise noted, my initial thought was that the site needed to update each page of the AE log CRF to add a line saying that relationships were documented by the site to be related to the regimen and not to the drug itself, unless otherwise noted. I felt more was needed and this prompted me emailing the GCP group.

My question is, given the AE logs are not source documents (the site has their source documentation of AEs locally and they transcribe the AEs onto our CRFs), does it seem acceptable to have our CRF reference a relationship column to the study drug and a query response for the site noting that the relationships were actually documented based on the regimen and not the study drug, unless otherwise noted, if the PI of the study signs and dates the query response to confirm this? In reviewing the GCP guidance I felt this may align with 4.91 (having the PI review each) and 4.92 (providing an explanation of discrepancy). While I do understand that the query response with the PI signature is considered a source document, I was unsure about the discrepancy between the CRF document outlining relationships to the study drug vs a query response noting that when the site documented relationships, they were not to the study drug as denoted by the column, and rather they were to the regimen. I did feel the older forms which just said "study treatment" were sufficient in conjunction with the query reply, however, but was unsure about the query responses related to the newer forms.

In short, I am looking for guidance on if the FDA feels it is sufficient documentation to only have the query response (signed by the PI) noting that the relationships are to the regimen and not the drug, unless otherwise specified, or if the FDA feels that changes or a comment is also needed on the actual CRF? Given the broadness of 4.91 and 4.92 in the GCP guidance this may be acceptable, but again I just want to be sure we have everything documented in the best manner.

Thanks very much