From: OC GCP Questions
To: [redacted] OC GCP Questions
Subject: RE: Operational accidental unblinding
Date: Thursday, May 28, 2015 1:49:00 PM

Dear [redacted] -

Doreen is out of the office this week, but I will respond to your additional question and copy Doreen so she is aware of the additional response I am providing.

Your question appears to be asking whether or not a sponsor can hire a single CRO to conduct both blinded and unblinded tasks on a blinded clinical trial.

FDA's IND regulations found at 21 CFR 312.52 (see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.52) state:

> *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.*

So sponsors are permitted by the regulations to transfer responsibility for **any or all** of the obligations in the regulations at 21 CFR 312 to a CRO and this transfer must be in writing (e.g., a negotiated contract or written agreement between the sponsor and the CRO). A sponsor may wish to address in the contract/written agreement their expectations for the CRO maintaining the blind when the CRO will conduct both blinded and unblinded tasks on a given study. The contract/written agreement should ensure compliance with all applicable laws and regulations relating to the conduct of the study, good clinical practice, health information privacy, etc. Your legal counsel would be best to consult with your specific question as FDA cannot offer legal advice.

FDA does not have specific guidance on transfer of regulatory obligations in clinical trials, however, sections 5.1 and 5.2 of the ICH GCP E6 Good Clinical Practice: Consolidated Guidance, (which is recognized as official FDA guidance – see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf) address sponsor responsibilities for quality assurance and quality control, as well as working with a CRO.

As Doreen previously mentioned, accidental unblinding can compromise the integrity of a study. If you would like to report serious noncompliance for an FDA-regulated drug study, you can report this information to CDER-OSI@fda.hhs.gov. If you want to report a complaint related to an FDA-regulated clinical trial, please see the following web page for information http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ComplaintsrelatingtoClinicaltrials/default.htm.

I hope this information is useful. If you need further information and/or have additional questions, please feel free to contact us at the official GCP mailbox, gcp.questions@fda.hhs.gov. You may also find it useful to access the set of redacted GCP e-mails found at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriestoFDAonGoodClinicalPractice/default.htm since we find that many questions and concerns are repeated over time.

Best Regards,

Janet

Janet Donnelly, RAC, CIP
Policy Analyst, Office of Good Clinical Practice
Office of Special Medical Programs, Food and Drug Administration

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From: [redacted]
Sent: Tuesday, May 26, 2015 8:19 AM
To: [redacted]; OC GCP Questions
Subject: Re: Operational accidental unblinding

Dear Doreen,

Hope you had a great holiday weekend.

I am still expecting the advice from the agency for our future practice dealing with the contract that contains unblind/blind conflict.

Should the double-blind trial sponsor be allowed to contract both of their unblinded monitoring and blind tasks with one CRO, any IGH GCP compliance issue here? Should CRO accept this kind of contract with the conflict?

This kind of contract conflict creates the unblind/blind conflict in the trial operation/management and creates the risk of operational accidental unblinding. From what I have experienced in the past, I think it is not a good practice for ensuring the study blind and integrity of the study data of double-blind clinical trials. I hope that the agency would regulate the conflict practice.

Please advise.

Thanks,
[redacted]

From: [redacted]
To: OC GCP Questions <gcp questions@fda hhs gov>
Sent: Wednesday, April 15, 2015 1:33 PM
Subject: Re: Operational accidental unblinding

Dear Doreen,

Thanks for your email, your advice, and the general information.

You mentioned "Accidental unblinding can compromise the integrity of the study." Thanks for the conclusion of accidental unblinding. I would also like to have a guidance at the practical level.

Should the sponsor be allowed to contract one CRO for both unblind and blind tasks for their double-blind study? Is there any ethical issue here?

If we can get a definite advice on this, we will definitely know what to do.

Please advise.

Thanks,
[redacted]

From: OC GCP Questions <gcp questions@fda hhs gov>
To: [redacted]
Sent: Wednesday, April 15, 2015 12 06 PM
Subject: Operational accidental unblinding

Good afternoon --

Below is general information regarding monitoring and blinding Accidental unblinding can compromise the integrity of the study

Generally, the study site monitor and CROs does not need to be aware of study arm assignments in order to fulfill site monitoring responsibilities Although the site monitor and or CRO does not have a role in study outcome assessment, he/she will be interacting with the site staff There is the potential that information may unintentionally be revealed that could break the blind for study staff In order to avoid such a possibility, individuals whose roles do not require knowledge of study arm assignments should be kept blinded If a monitor discovers findings where unblinding may be needed, he/she should contact the sponsor who would determine how to proceed with those findings while maintaining the study's integrity

The ICH E-6 Good Clinical Practice Consolidated Guidance, an FDA official guidance, addresses Randomization Procedures and Unblinding in Section 4 7

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

4 7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e g , accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s)

Since you stated that the studies involve FDA-regulated drug products under IND, you can report serious non-compliance to the Center for Drugs (CDER) Office of Compliance Please see their email below

CDER-OSI@fda hhs gov

I hope this information is helpful Please contact us again at gcp question@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, April 14, 2015 4:30 PM
To: OC GCP Questions
Subject: Re: Operational accidental unblinding

Dear Doreen,

Thanks for your quick reply.

Yes, the studies involve FDA-regulated drugs and biologics (no devices) under INDs.

Thanks,

[redacted]

From: OC GCP Questions <gcp questions@fda hhs gov>
To: [redacted]
Sent: Tuesday, April 14, 2015 3:59 PM
Subject: Operational accidental unblinding

Good afternoon --

Your email was forwarded to my office for a response. Can you tell me if the study involves an FDA-regulated product, is under IND/IDE and does it involve a drug, device, or biologic?

Thank you,

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

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[redacted]

Comments: Dear FDA Officer,

I have a serious question. At least I think it is serious.

In the Recent years, I see the CROs start to receive trial contracts from double-blind trial sponsors with both blinded and unblind tasks in the same contract. In the beginning, I thought that was a trust from the sponsor.

During the operation of the trials, the operational accidental unblinding (OAU) incidents started happening. Some incidents may potentially cause the entire trial failure. The OAU incidents could not be stopped even by applying SOPs to the process. SOPs just don't work on stopping accidents. It is very credential damaging to CRO's success if the CROs report each incident to the sponsor. Currently, sponsors continue to grant this kind contract to CROs and CROs continue to take this kind contracts. This kind contract makes the sponsor easier on contracting and gives the money making an opportunity to CRO. Everybody is happy now.

I realize that this kind contract creates a serious problem, a blind/unblind crossover/self-conflicting trial operation structure. I think it is a conflict of interest and it is a malpractice on double-blind trial operation. This kind defective operational system provides the opportunity for the risk of operation accidental unblinding at such a high operational level and may damage the integrity of the blind

of double-blind clinical trials.

I would know if this kind contract with the conflict of interest is allowed in principle by CGP?

Looking forward to your official advice.

Thanks,

[redacted]