From: OC GCP Questions
To: [redacted]
Subject: RE: Oversight of IRB submissions
Date: Monday, March 23, 2015 10:00:00 AM

Dear [redacted] -

Thank you for the clarification and my apologies for the delay in my response. As I understand your response, as a sponsor, you might use a notification letter process as a form of immediate notification to the investigators about a change to the protocol that is immediate and necessary to eliminate an apparent immediate hazard to the subjects (e.g., you mentioned, a change in eligibility criteria, or an additional safety test for a newly identified AE). Lets call this scenario #1. In scenario #1, the notification letter is considered a change in research/change to the protocol. The investigator has regulatory responsibilities for handling changes in research. As a sponsor, you should ensure your investigators follow the applicable regulations for handling changes in research/changes to the protocol, including immediate changes made to eliminate an apparent immediate hazard to subjects. The regulatory responsibilities for handling changes in research for investigators, IRBs, and sponsors are described below.

You also mentioned that as the sponsor you might send the investigator a notification letter to inform them of a future change to the protocol that is not an immediate safety concern. So, I have to assume that in this case, the notification letter is **NOT** serving as the official change/amendment to the protocol, is **NOT** providing instructions of the changes to make, but rather, the notification letter is serving as general correspondence describing a change to the protocol that is forthcoming in the form of a protocol amendment. Lets call this scenario #2. In scenario #2, the sponsor is **NOT** instructing the investigator to implement a change yet, but is simply informing the investigator that an amendment will be forthcoming. If this assumption is true, the notification letter in scenario #2 is likely **NOT** considered a change in research/change to the protocol and there would not be a regulatory requirement for the investigator to submit this to the IRB. However, some investigator's IRBs may want to be notified of such information. Whether or not the investigator must submit this type of general correspondence to their IRB likely depends on the investigator's and the IRB's Standard Operating Procedures (SOPs). Each investigator needs to be familiar with and follow their SOPs and IRB requirements. As a sponsor, you should be familiar with the process your investigators will follow for handling this type of information since the investigator must be compliant with their SOPs and IRB requirements.

However, if as the sponsor you are using a notification letter as the actual mechanism to implement an official change/amendment to the protocol, and the letter is instructing the investigator to make a specified change to the protocol (i.e., the notification letter serves as the amendment to the protocol to be appended to the current protocol), then this would be considered a change in research/change to the protocol that must be submitted to the IRB for approval prior to implementation. Lets call this scenario #3. I don't think you are describing scenario #3 in your question, but I wanted to address it just in case. (**NOTE:** This mechanism for amending a protocol via a letter appended to the protocol is not preferable. It is preferable that sponsors issue an amended protocol to implement changes to the protocol). As a sponsor, you should ensure your investigators follow the applicable regulations for handling changes in research/change to the protocol, including immediate changes made to eliminate an apparent immediate hazard to subjects. The regulatory responsibilities for handling changes in research for investigators, IRBs, and sponsors are described below.

Generally, sponsors prepare protocol amendments to address changes in the protocol. The type of changes you mentioned (adding a biomarker test, or adding an additional analyte to a blood panel, or adding a few more patients to a cohort) usually do not qualify as changes that must be made to eliminate an apparent immediate hazard to subjects, so these types of protocol changes are best made via an amended protocol. Properly amending the protocol should help to ensure that your investigators are compliant with both submitting amendments to their IRB, and following the correct version of the protocol.

The investigator regulations at 21 CFR 312.66 require that investigators not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. The device regulations for investigators at 21 CFR 812.150(a)(4) are similar.

Investigators have a regulatory responsibility to get IRB approval for changes as stated in the regulations. As you previously mentioned, sites may have SOPs that outline the process they follow for submitting changes in research activities/changes in protocols to their IRB. These SOPs may vary from site-to-site, so it is important that each investigator is familiar with and follows their SOPs. In addition, investigators need to follow their IRB requirements for changes in research/changes in protocols. As a sponsor, you should ensure your investigators follow the applicable regulations for handling changes in research/change to the protocol, including immediate changes made to eliminate an apparent immediate hazard to subjects since the investigator must be compliant with the regulations and the IRB requirements.

The IRB regulations at 21 CFR 56.108(a)(3) and (4) require the IRB to follow written procedures for ensuring prompt reporting to

the IRB of changes in research activity, and for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

The IRB regulations provide IRBs flexibility in how they develop their written procedures for handling changes in research, including those that require prior submission and approval, and those changes made to eliminate an apparent immediate hazard to human subjects. The IRB written procedures may vary from IRB-to-IRB, so again, it is important that each investigator is familiar with and follows their IRB's requirements. As a sponsor, you should ensure your investigators follow the applicable regulations for handling changes in research/changes to the protocol, including immediate changes made to eliminate an apparent immediate hazard to subjects since the investigator must be compliant with the regulations and the IRB requirements.

The sponsor regulations in both 21 CFR 312 subpart D and 812 subpart C address sponsor responsibilities, including but not limited to, choosing qualified investigators, providing investigators with the information they need to conduct the investigation properly, reviewing ongoing studies and ensuring proper monitoring. If a sponsor discovers that an investigator is not in compliance with the signed agreement, the investigational plan, the regulations, and as stated in the device regulations, any conditions of approval imposed by the reviewing IRB or FDA, the sponsor must either secure compliance, or terminate the investigator's participation.

So, the regulations are clear that investigators are responsible for not initiating changes in research without prior IRB review and approval except where necessary to eliminate apparent immediate hazards to subjects.

Sponsors have responsibilities for reviewing ongoing studies and ensuring proper monitoring to ensure compliance, so sponsors should ensure that investigators do not initiate changes without IRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects. The sponsor's responsibility to ensure that their investigators are compliant with seeking IRB approval of changes in research is no different than the sponsor's responsibilities to ensure investigators are compliant with all other applicable regulations.

The regulations provide sponsors flexibility in how they choose to carry out their regulatory responsibilities for ensuring and/or securing compliance at investigator sites. Sponsors are free to develop their own procedures and practices as long as applicable regulatory requirements are met. There are likely many ways a sponsor can ensure compliance at the investigator site for changes in research. For this reason, there is not one right answer for you. FDA has guidance titled, "Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring" that can be found at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm269919.pdf. Also, the ICH GCP E6 Good Clinical Practice: Consolidated Guidance, (which is recognized as official FDA guidance and can be found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf) discusses sponsor monitoring in section 5.18.

You may want to discuss this issue with the appropriate representatives at your sponsor company to ensure that there is a clear and consistent process at your company. You may want to discuss the most efficient mechanism by which your sponsor company can ensure investigator compliance with the regulatory requirements for changes in research.

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

---

From: [redacted]

Sent: Friday, March 13, 2015 7:37 AM
To: OC GCP Questions
Subject: RE: Oversight of IRB submissions

Sorry for not being clear.

It really could be either. One, a letter informing them of an immediate need to change something required for safety (change in eligibility criteria or an additional safety test for a newly identified AE) that will be followed by a protocol amendment. The other is a letter informing the PI of a future change in the protocol that is not an immediate safety concern, eg adding a biomarker test or adding an additional analyte to a blood panel or adding a few more patients to a cohort that can be implemented within the current approved ICF/protocol. The expectation is that for the immediate safety issue, investigators will inform their IRB immediately but the question is the same in that how much verification, source documentation etc is needed or should be sought by the sponsor to ensure that the letter has been sent to and acknowledge by the IRB. Is documenting the informing of the investigator and the acknowledgement by the investigator they have read the letter and understand the implication sufficient for appropriate oversight, with the expectation that they will fulfill any institutional and IRB reporting requirements as an internal matter?

Hope that clarifies the question.

Regards,

[redacted]

From: OC GCP Questions [mailto:gcp.questions@fda.hhs.gov]
Sent: Thursday, March 12, 2015 6:19 PM
To: [redacted]
Subject: RE: Oversight of IRB submissions

Dear [redacted] -

Thank you for your question. However, based on the limited information provided, I am not able to provide you with thoughts on a response because it is not clear what you mean when you refer to a "notification letter".

Your question mentions a "notification letter" prepared by the sponsor informing the investigator of a change in the protocol or a safety test that needs to be implemented while a formal protocol amendment is being written. It is not clear what you mean by a "notification letter" as the FDA regulations do not address this terminology.

Generally speaking, sponsors prepare a protocol amendment to address changes in the protocol, unless there is a need to make an immediate change to eliminate apparent immediate hazards to the human subjects, in which case, the sponsor may utilize a more immediate type of notification to investigators, and follow up with a protocol amendment. Is this the scenario you are referring to when you talk about a "notification letter"? In other words, is your term "notification letter" referring to a type of **immediate notification** to investigators in a scenario where this is a need for the sponsor and investigator to make an immediate change to eliminate an apparent immediate hazard to human subjects? Please provide more information or a clarification on what you mean by "notification letter" and the scenario you are referring to.

Also, I wanted to mention that the FDA regulations do not address contracts between sponsors and IRBs, however, FDA has guidance titled, "Institutional Review Boards Frequently Asked Questions – Information Sheet" that addresses communications between sponsors and IRBs (see http://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm question #30, copied here for reference):

> **30. Does FDA prohibit direct communication between sponsors and IRBs?**
>
> It is important that a formal line of communication be established between the clinical investigator and the IRB. Clinical investigators should report adverse events directly to the responsible IRB, and should send progress reports directly to that IRB. However, FDA does not prohibit direct communication between the sponsor and the IRB, and recognizes that doing so could result in more efficient resolution of some problems.
>
> FDA does require direct communication between the sponsors and the IRBs for certain studies of medical devices and when the 21 CFR 50.24 informed consent waiver has been invoked. Sponsors and IRBs are required to communicate directly for medical device studies under 21 CFR 812.2, 812.66 and 812.150(b). For informed consent waiver studies, direct communication between sponsors and IRBs is required under 21 CFR 50.24(e), 56.109(e), 56.109(g), 312.54(b), 312.130(d), 812.38(b)(4) and 812.47(b).

So FDA does not prohibit direct communication between sponsors and IRBs, but sponsors should keep investigators informed of any communications they have with an investigator's IRB in the spirit of keeping the investigator informed.

I look forward to your response and clarification.

Best Regards,

Janet

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

---

From: [redacted]
Sent: Tuesday, March 10, 2015 3:58 PM
To: OC GCP Questions
Subject: Oversight of IRB submissions

I understand that unless there is a specific contract between a sponsor and an IRB, the usual communication flow is between the Institution/PI and the IRB. When a sponsor provides a notification letter informing the PI of a change in the protocol or a safety test that needs to be implemented (while a formal protocol amendment is being written), to what extend does a sponsor need to actively ensure and source document verify that the information has been submitted to the IRB? Sites are often slow in acknowledging or confirming that these letters have been forwarded. Sometimes email affirmation is all that is provided, with no real "proof" and sometimes the sites own regulations determine the timing and sorts of notification. Is it the sponsor responsibility to insist that the site submit to their IRB within a certain timeframe and is there an obligation on the part of the sponsor to track and verify submissions have occurred?

Regards,

[redacted]