From: OC GCP Questions
To: [redacted]
Subject: RE: Institutional Review Board Protocol/Amendments/Informed Consent Form Signed Approval Letters
Date: Monday, April 21, 2014 7:39:00 PM

Dear [Redacted] –

Thank you for your question. With regard to IRB approval, the FDA regulations at 21 CFR 56.109(a) state:

> *Sec. 56.109 IRB review of research.*
>
> *(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.*

The regulations at 21 CFR 56.109(e) state:

> *(e) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. For investigations involving an exception to informed consent under 50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under 50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.*

The regulations do not address any requirement for the IRB to sign the written notification. When the regulations are silent, IRBs and institutions are free to develop their own procedures and practices as long as applicable regulatory requirements are met.

ICH GCP E6 Good Clinical Practice: Consolidated Guidance, (which is recognized as official FDA guidance) mentions IRB/IEC approval in a few sections (you can access this guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf):

> **1. GLOSSARY**
>
> 1.5 Approval (in relation to institutional review boards (IRBs)): The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, good clinical practice (GCP), and the applicable regulatory requirements.
>
> **3.1 Responsibilities**
>
> 3.1.2 The IRB/IEC should obtain the following documents:
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> Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may require to fulfil its responsibilities.
>
> The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed, and the dates for the following:
>
> - Approval/favorable opinion;
> - Modifications required prior to its approval/favorable opinion;
> - Disapproval/negative opinion; and
> - Termination/suspension of any prior approval/favorable opinion.
>
> **4.4 Communication with IRB/IEC**
>
> 4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment

procedures (e.g., advertisements), and any other written information to be provided to subjects.

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

8.2.7 Dated, documented approval/favorable opinion of IRB/IEC of the following:

- Protocol and any amendments
- CRF (if applicable)
- Informed consent form(s)
- Any other written information to be provided to the subject(s)
- Advertisement for subject recruitment (if used)
- Subject compensation (if any)
- Any other documents given approval/favorable opinion

To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s).

The ICH GCP E6 document provides some guidance on what should be included in the IRB written notification with regard to referencing what the IRB reviewed and the IRB's action (e.g., clearly identifying the trial, the documents reviewed, the IRB's decision, and the date of that decision). However, this guidance does not specify that the IRB must sign the written notification.

FDA also has Information Sheet Guidance for IRBs – Frequently Asked Questions that can be found at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm. Question #29 under section III addresses signing IRB written notification of approval. This guidance states:

III. IRB Procedures

29. Does FDA expect the IRB chair to sign the approval letters?

FDA does not specify the procedure that IRBs must use regarding signature of the IRB approval letter. The written operating procedures for the IRB should outline the procedure that is followed.

So, as you can see, the FDA does not specify the procedure IRBs must use for written notification of approval, but instead provides IRBs flexibility.

The IRB approval notification should be clear about which IRB approved which study; what was approved by the IRB, and when the approval was granted. I recommend that if you find that certain IRB approval letters are not clear that you contact that IRB and discuss your concerns with them.

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

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Office of Special Medical Programs, Food and Drug Administration

From: [Redacted]
Sent: Thursday, April 17, 2014 5:52 PM
To: OC GCP Questions
Subject: Institutional Review Board Protocol/Amendments/Informed Consent Form Signed Approval Letters

We are a niche Clinical QA Consulting Firm, currently performing audits and consulting services for a large number of Pharmaceutical Companies. It has been recently noted by monitors and auditors that IRB approvals (both Central and Local) on file at investigator sites as unsigned notifications rather than signed IRB approval letters. Clients are questioning the appropriateness of this practice and are uncomfortable – especially from an auditing perspective, as the internal IRB Meeting Minutes are not documents that would be available to Auditors at Investigator Sites. Also, IRB policies regarding this are not available to QA auditors.

IRB approval notifications without signatures or dates stamps of approval represent a major change to industry best practice in the GCP arena. The argument from Central IRBs is that FDA regulatory requirements use the term "notification" of approval and do not stipulate a signed approval letter. Yet from an auditor's perspective it would seem very easy to develop a forged IRB approval.

Please comment regarding the perspective of the FDA regarding IRB approvals with no signatures or official stamps of approval?

Thank you for your attention to this inquiry.

[Redacted]