From: Lee, Bonnie
Sent: Tuesday, April 05, 2005 4:08 PM
To: [Redacted]
Cc: Lepay, David
Subject: RE: IBs

Dear [Redacted] ,

Julie is correct that there is no requirement in FDA's regulations for the IRB to review the investigator's brochure (IB); however, there is information in the IB that the IRB would need to consider when approving research. Further, as you know, the IRB is responsible for ensuring that changes in approved research are not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 56.108(a)(4)); and for ensuring prompt reporting to the IRB...of (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance....; etc. (21 CFR 56.108(b)). If the IRB is provided with the necessary information to carry out these responsibilities without the IB, then it seems unnecessary to review the IB unless the sponsor highlights the changes and believes that the changes in the IB require IRB review and approval before being initiated because those changes have not previously been submitted to the IRB for review and approval. I agree with you that just "noting" receipt of the IB seems pointless.

I hope this is helpful to you.

Sincerely,

Bonnie

Bonnie M. Lee
Associate Director for Human Subject Protection Policy
Good Clinical Practice Program, FDA

-----Original Message-----
From: [Redacted]
Sent: Tuesday, April 05, 2005 3:49 PM
To: blee@oc.fda.gov; dlepay@oc.fda.gov
Subject: Fw: IBs

Could either of you please comment on the situation we're dealing with here? As I read through the proposal again, I'm wondering if we should even receive these. If they're just "noted", they're not being reviewed so why ask for them at all? Please advise how you think revised IBs should be handled, especially when there is no summary of changes. Thank you for your time and expertise.

[Redacted]
----- Forwarded by [Redacted] on 04/05/2005 01:08 PM -----

"Kaneshiro, Julie A" <JAKaneshiro@OSOPHS.DHHS.GOV>

04/05/2005 11:02 AM

To [Redacted]

cc "Stith-Coleman, Irene" <IStithCo@OSOPHS.DHHS.GOV>, "Carome, Michael" <MCarome@OSOPHS.DHHS.GOV>, "Borror, Kristina" <KBorror@OSOPHS.DHHS.GOV>, "Drew, Glen" <GDrew@OSOPHS.DHHS.GOV>, "Gorey, Julia" <JGorey@OSOPHS.DHHS.GOV>, "Prohaska, Kevin (OPHS/OHRP)" <KProhask@OSOPHS.DHHS.GOV>, "Odwazny, Laura M. (OS)" <LOdwazny@psc.gov>, "Hicks, Shirley" <SHicks@OSOPHS.DHHS.GOV>

Subject RE: IBs

Hi [Redacted] ,

After discussing your question with some colleagues here at OHRP, we agree with your proposal regarding changes to Investigator Brochures. There is no regulatory requirement in 45 CFR part 46 that requires IRBs to "approve" IBs, but the IRB can certainly consider information in the IB when deciding whether to approve a research protocol using a test article described in the IB.

Since the studies in question would also be regulated by FDA, you might want to ask FDA for their views on this as well. I think Bonnie Lee (blee@oc.fda.gov) or Dave Lepay (dlepay@oc.fda.gov) would be appropriate contacts. Note that FDA's current information sheet on "Charging for Investigational Products" states the following:

> "There is no specific regulatory requirement that the Investigator's Brochure be submitted to the IRB. There are regulatory requirements for submission of information which normally is included in the Investigator's Brochure. It is common that the Investigator's Brochure is submitted to the IRB, and the IRB may establish written procedures which require its submission. Investigator's Brochures may be part of the investigational plan that the IRB reviews when reviewing medical device studies."

I hope this helps. Just let me know if you have any questions.

Julie

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From: [Redacted]
Sent: Monday, April 04, 2005 2:57 PM
To: Kaneshiro, Julie A
Subject: IBs

Julie,
Sorry, I've got another question for you (hopefully this one's as easy as the last!).

We have been having a lot of trouble lately with people who can't seem to get a list of changes from their sponsor when they send in revised Investigator Brochures (this seems to happen most often with the cooperative groups). Holding for the list of changes can cause significant delays and, as a result, hold up the review of consent form changes or other changes that might impact patient safety. We have been told that the IB is the last thing to be changed when a sponsor identifies a new risk associated with the drug. For example, if multiple patients experienced the same SAE and it had been determined to be directly related to the study drug, before the IB would be revised the sponsor would:

- report the SAEs
- modify the consent (as appropriate)
- if applicable, send a letter to participants no longer receiving treatment
- modify the protocol (as appropriate)

There are some protocol sponsors (eg the cooperative groups) that do not even require that their PIs submit revised IBs to the IRB (however, the IRB requires submission).

Since we would see paperwork associated with each of these actions, can we "note" rather than "approve" IBs? This way, if the revised IB is not accompanied by a list of changes, we can "note" that the IB has been

revised, but do not have to be concerned about "approving" something when we are unsure of the changes.

This was the best of our brainstorming on how to handle this situation. If there's another way you think would be better for handling these, we're all ears. Thanks so much for being such a great resource, I'm definitely going to miss you while you're on leave!

[Redacted]