From: OC GCP Questions
To: [redacted]
Subject: RE: informed consent question
Date: Thursday, September 17, 2015 2:20:40 PM

Based on the limited information you provided, I do not believe it is unreasonable for the phrase "significant risk" to be used to describe risks associated with a research protocol deemed by an IRB to be "more than minimal risk." The phrase "more than minimal risk" is a regulatory phrase that encompasses any risk thought to be more than minor, including significant and serious risks. I do not understand why the local IRB did not have access to aggregated safety data (as you state); it is the responsibility of the investigator to provide the IRB with the appropriate information they need to make their determinations. Putting that aside for a moment, it must be remembered that investigational drugs often have unknown risks that can be significant. Alerting prospective subjects and the LARs to this possibility does not seem unreasonable to me and does not seem to purposefully misinform the subject. It appears your concern may be with an institutional policy being enforced by an Institutional Official rather than the local IRB. As a general rule, FDA regulations do not govern institutional policies and we do not get involved with Institutional Official actions related to IRB matters unless the Institutional Official unduly influences the decisions of the IRB. If you believe the Institutional Official is unduly influencing the decisions of the IRB, or believe the local IRB was not provided with sufficient information to make their determinations, then you may submit a complaint to CDER-OSI-GCPReferrals@fda.hhs.gov (assuming this is a drug product). Additionally, you may also want to contact the FDA review division responsible for the clinical investigation if you continue to believe the risk associated with the research is being mischaracterized.

On a final note, your statement that there is "no known, effective treatment for Alzheimer's disease" is inaccurate and would be misleading if this is stated to prospective subjects either in the informed consent document or during the informed consent process. FDA has approved several drug products for the treatment of Alzheimer's disease. Although they each have their limitations, they have been found to be safe and effective for the treatment of Alzheimer's disease.

I hope this information is helpful to you. If further assistance is needed, please feel free to contact us once again at the official OGCP mailbox, gcp.questions@fda.hhs.gov

Thank You,

Kevin

Kevin A. Prohaska, D.O., M.P.H., Captain (USPHS)
Senior Medical Policy Analyst
Office of the Commissioner
Office of Good Clinical Practice

From: [redacted]
Sent: Tuesday, September 15, 2015 5:38 PM
To: OC GCP Questions
Subject: Re: informed consent question

Kevin -

Thank you for your speedy reply. To help clarify my question I have attached the capacity assessment section of the informed consent document. The issue is not about conducting a capacity assessment of the prospective subject, but suggesting to the subject that the study is 'significant risk' and the LAR would consent to the subject's participation. The capacity assessment is only for this study as seen on page 3 of the assessment. At the top is the statement; "You are being asked to participate in the research project named above." and at the bottom *"I agree to participate in the research protocol named above. I hereby choose a person I trust to make decisions about participation in this study for me."*
The local IRB did review this protocol and agreed with the central IRB finding of 'more than minimal risk'. The reference to 'significant risk' in the capacity assessment was not an IRB decision. This was a policy of the Institutional Official.

The local IRB does not have access to aggregated safety data to determine whether the study is ‘significant risk’ and more than likely would not approve a 'significant risk' study. This is the responsibility of the sponsor. Outlined in 312.32 IND safety reporting: (ii) Findings from other studies. The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

To reiterate, my concern with referencing this clinical trial as 'significant risk' is it seems to purposely misinform prospective subjects and their LARs. There is no known, effective treatment for Alzheimer's Disease so despite any serious misgivings or anxiety about a 'significant risk' clinical trial subjects will take part and their LARs will consent. Is it really necessary to frighten these people?

On 9/15/2015 6:41 AM, OC GCP Questions wrote:

> Thank you for bringing your concern to FDA’s attention. I am not exactly certain what question you are asking, but presumably you want to know whether what the local Institutional Review Board (IRB) is doing is acceptable from FDA’s perspective. FDA generally give IRBs wide latitude in determining the level of risk they believe a given protocol entails and in determining whether capacity assessments should be part of the informed consent process. FDA regulations do not define “significant risk” nor does it describe when capacity

assessments should be done. Given the protocol you briefly outlined involves a condition characterized by progressive dementia, it does not seem unreasonable to me for the local IRB to require a capacity assessment be included in the informed consent process. Likewise, given the potential unknown risks associated with an investigational drug product, it does not seem unreasonable to me for a local IRB to characterize the risk as significant. This is especially true for an investigational drug product that will likely need to be taken long-term, as is often the case for conditions such as Alzheimer's disease.

It is not possible for me to assess the "suitability" of the informed consent document without actually reviewing the informed consent document and the associated protocol materials; however, the language you provide about the informed consent document (i.e., "*the LAR that he or she names can consent to their participation in 'significant risk' clinical trials*") suggests the IRB wants to assure prospective subjects understand the extent of the LARs authority. Although it would be a matter of state and local law, it is likely the authority of the LAR extends to all subsequent clinical research decisions related to the trial in question and could allow the LAR to consent to the individual's participation in future unknown clinical investigations. It does not seem unreasonable to me for the IRB to require that prospective subjects be alerted to the extent of the LARs authority.

I hope this information is helpful to you. If further assistance is needed, please feel free to contact us once again at the official OGCP mailbox, gcp.questions@fda.hhs.gov

Thank You,

Kevin

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301-796-3707

From: [redacted]
Sent: Saturday, September 12, 2015 8:58 AM
To: OC GCP Questions
Subject: informed consent question

I am contacting the Office of Good Clinical Practice to inquire about the suitability of an informed consent document in use at a local site for a multi-site clinical trial of an IND for Alzheimer's Disease. A local site requirement is that a psychiatrist will determine whether the prospective subject has capacity to name a Legally Authorized Representative (LAR).

The informed consent document includes a section for this determination along with informing the prospective subject that the LAR that he or she names can consent to their participation in 'significant risk' clinical trials. The informed consent document does not provide a definition of 'significant risk' and the capacity assessment determination is for this single clinical trial.

The local investigator communicated a question from the sponsor to the Institutional Official (IO) designate about the reference to 'significant risk'. The explanation provided by the designate is that this requirement is according to the policies and procedures in the IRB Manual. The designate also explained that; "The language is to alert the prospective subject that the LAR can consent to any risk level research including research that involves 'significant risk' and that 'Greater than minimal risk' does not accurately convey this required concept." The consent document is for this one trial which is greater than minimal risk.

From a regulatory perspective the only reference to a 'significant risk' IND is in Sec. 312.32 IND safety reporting: "The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug." There is no NY State statute addressing 'significant risk' clinical trials.

While this clinical trial is greater than minimal risk, the IO designate states that it is a requirement to reference the trial as 'significant risk'. In reality there is no known, unusual clinical toxicity associated with the study drug. The trial has been underway for some time and no significant potential for serious risk to human subjects has developed. To reference this clinical trial as 'significant risk' seems to purposely misinform prospective subjects (vulnerable population) and their LAR. There is no known, effective treatment for Alzheimer's Disease so despite any serious misgivings or anxiety about taking part in a 'significant risk' clinical trial prospective subjects and LARs will likely consent to participate.

Thank you for you insights on this matter.