From: OC GCP Questions
To: [redacted]
Subject: informed consent question
Date: Monday, September 21, 2015 8:05:11 AM

Good morning [redacted] –

Many of our OGCP staff members respond to questions in our GCP queries box. Our query process is a non-binding informal guidance that is used to answer questions that the public might have related to FDA regulations and Good Clinical Practice. All queries are redacted by year and posted on FDA's website. I have included the link below to our GCP website. Here you will find many helpful links.

Clinical Trials and Human Subject Protection

Kind regards,

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

From: [redacted]
Sent: Thursday, September 17, 2015 7:56 PM
To: OC GCP Questions
Subject: Re: informed consent question

Kevin - Again thanks for your speedy reply. Sponsors are specifically required to notify all participating investigators (and FDA) in a written IND safety report of "any adverse experience associated with the use of the drug that is both serious and unexpected" and "any finding from tests in laboratory animals that suggests a significant risk for human subjects" (§ 312.32(c)(1)(i)(A),(B)). The local investigator for this multi-site study has not been notified of any findings that suggest a significant risk for human subjects or been notified by the sponsor that FDA has placed the study on a clinical hold because of a significant risk determination. A local IRB does not receive aggregate safety data, but rather recommendations from the Data and Safety Monitoring Board (DSMB) based an analysis of the safety data.

The assessment of risks and benefits for a study requires a careful array of all relevant data. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity

(magnitude) of the envisioned harm.

As you suggest investigational drugs often have risks that can be significant, but the issue is frequency of significant risks which when high is the basis for FDA to place a clinical trial on hold. Two informed consent elements required by the regs: "A description of any reasonably foreseeable risks or discomforts to the subject; For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained." There is no regulatory requirement to state 'greater than minimal risk' or 'significant risk' in the consent form. Alerting prospective subjects and the LARs to the possibility of significant risk does not have merit; there is no evidence to support the reference. How many NCI clinical trials reference that the trial is 'significant risk' for subjects? None. How many IRBs will approve a study that presents 'significant risk' to subjects? None.

The IOs requirement to inform the prospective subject that the LAR will consent to his or her participation in a 'significant risk' clinical trial is a policy for all clinical trials involving a LAR. It is not driven by any safety data findings or regulatory requirements. The reference to 'significant risk' says nothing about any foreseeable risks or discomforts to the subject.

Is this an official FDA position on the use of 'significant risk'? Can I reference our email exchange with other people?

The statement that there is "no known effective treatment for Alzheimer's Disease" is not told to prospective subjects and as you correctly point out is inaccurate. FDA has approved two classes of drugs for treating Alzheimer's disease: cholinesterase inhibitors and partial glutamate antagonists. Neither class of drugs has been proven to slow the rate of progression of Alzheimer's disease.

[redacted]