From: Lee, Bonnie on behalf of OC GCP Questions
Sent: Wednesday, September 08, 2004 12:21 PM
To: **[Redacted]**
Subject: RE: QUESTION RELATED TO FDA REGULATIONS ON PATIENT WAIVERS

Dear **[Redacted]**,

Let me provide some clarification to your questions:

1. Are patient waivers (as described above) be viewed as a "change in approved research" and therefore require IRB approval before implementation?

Yes. If the change is a "minor change in previously approved research during the period for which approval is given" then is could be reviewed by the IRB through an expedited review process; otherwise, it would require full committee review.

2. Are patient waivers without IRB approval considered a violation of the regulation?

Yes, unless the change was to "eliminate apparent immediate hazards to the human subjects."

3. Are there any instances where a patient waiver would be considered acceptable other than the situation to eliminate apparent hazard to the human subject? For example, would a waiver be considered acceptable if pre-approved by the IRB?

If exceptions were built into the protocol then presumably they would have been reviewed and approved by the IRB at the time it reviewed and approved that protocol. The language in 56.108(a)(3) and (4) are about changes in research that have not been "pre-approved" by the IRB. If the IRB has pre-approved the exceptions/waiver, then the exceptions are being done with IRB review and approval.

I hope this is helpful to you.

Bonnie

Bonnie M. Lee

Associate Director for Human Subject Protection Policy

Good Clinical Practice Program, FDA

-----Original Message-----
From: [Redacted]
Sent: Tuesday, August 31, 2004 8:36 AM
To: 'OC GCP Questions'
Subject: QUESTION RELATED TO FDA REGULATIONS ON PATIENT WAIVERS

Hello. I am seeking to more clearly understand the FDA regulations on the issue of patient "waivers" or exceptions to enrolling subjects who do not meet one or more of the protocol-defined entry criteria. There are two scenarios:

1. Prospective Waivers: Upon occasion, a site will phone the sponsor to inform them of a potential patient they wish to enroll in the study. The patient, however may not exquisitely meet one or more of the predefined entry criteria. The sponsor will review the criteria and may issue what is commonly referred to as a "waiver" or "exception" letter allowing the investigator to enroll the patient.

2. Retrospective Waivers: There is the second situation where a site enrolls a patient who does not meet the protocol criteria without sponsor prospective approval. This is only noted after the fact by the monitor. In such cases, the sponsor is notified and then provides a written acknowledgement to the site of this deviation and advise on whether the patient should be allowed to continue in the study.

In both cases, patients would ultimately be considered protocol violators for purposes of the statistical analysis, however may be allowed to continue in the study provided there are no safety concerns in allowing them to do so.

The only regulation I could locate that speaks to this topic is the following:

PROTOCOL CHANGES

21 CFR 56.108 (a)(3)&(4) [IRB follow written procedures] for ensuring prompt reporting to IRB of changes in research activity; and (4) 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.

Can I seek clarification on the following points;

1. Are patient waivers (as described above) be viewed as a "change in approved research" and therefore require IRB approval before implementation?

2. Are patient waivers without IRB approval considered a violation of the regulation?

3. Are there any instances where a patient waiver would be considered acceptable other than the situation to eliminate apparent hazard to the human subject? For example, would a waiver be considered acceptable if pre-approved by the IRB?

Thank you in advance for any insight you can provide to me on this subject.

Sincerely,

[Redacted]