From: Beers Block, Patricia on behalf of OC GCP Questions
Sent: Tuesday, January 20, 2004 10:58 AM
To: [purged]
Subject: RE: Question on Investigational Plans/IRBs

Dear [purged],

I've taken the liberty to extract material from the FDA's Information Sheets for IRBs and Clinincal Investigators in hope that this information will be responsive to your question and helpful to you. You can find this material by going to our GCP web page (www.fda.gov/oc/gcp) and selecting the heading "Guidances and Information Sheets". The information sheet collection is the very first entry on the Guidance web page (www.fda.gov/oc/ohrt/irbs/default.htm).
In selecting the following information, I'm making the assumption that your question relates to a significant risk device. The IRB should have written procedures that clarify what the IRB needs/expects when it reviews research studies. The information sheet provides the FDA's intrepreation of what the IRB needs to have available to it in order to properly review the research proposal and make a decision as to whether or not to approve the research. Information particularly responsive to your question can be found in the sections entitled "SR/NSR Studies and the IRB ; The NSR/SR Decision" and "Frequently Asked Questions about IRB Review of Medical Devices". Specifically, the IRB needs to have enough information available to it to make an informed decision about permitting the conduct of the study; under 21 CFR 56.108(a)(1) the IRB must follow its written procedures for conducting its initial review of research and for reporting its findings and actions to the investigator. The procedures followed in determining whether a study is SR or NSR should be included among those written procedures.
I hope the following information is helpful to you.

Patricia M. Beers Block
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Good Clinical Practice Programs
OSHC/Office of the Commissioner
301-827-3340
This communication does not constitute a written advisory opinion under 21 CFR 10.85, but rather is an informal communication under 21 CFR 10.85(k) which represents the best judgment of the employee providing it. This information does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

INFORMATION SHEETS
Guidance for Institutional Review Boards and Clinical Investigators
1998 Update

Medical Devices

Medical Devices

A medical device is defined, in part, as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for in vitro diagnosis (IVD) of disease and other medical conditions such as pregnancy.

Clinical investigations of medical devices must comply with the Food and Drug Administration (FDA) informed consent and Institutional Review Board (IRB) regulations [21 CFR parts 50 and 56, respectively]. Federal requirements governing investigations involving medical devices were enacted as part of the Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990. These amendments to the Federal Food, Drug, and Cosmetic Act (the Act) define the regulatory framework for medical device development, testing, approval, and marketing.

Except for certain low risk devices, each manufacturer who wishes to introduce a new medical device to the market must submit a premarket notification to FDA. FDA reviews these notifications to determine if the new device is "substantially equivalent" to a device that was marketed prior to passage of the Amendments (i.e., a "pre-amendments device"). If the new device is deemed substantially equivalent to a pre-amendments device, it may be marketed immediately and is regulated in the same regulatory class as the pre-amendments device to which it is equivalent. (The premarket notification requirement for new devices and devices that are significant modifications of already marketed devices is set forth in section 510(k) of the Act. Devices determined by FDA to be "substantially equivalent" are often referred to as "510(k) devices". If the new device is deemed not to be substantially equivalent to a pre-amendments device,

it must undergo clinical testing and premarket approval before it can be marketed unless it is reclassified into a lower regulatory class.

Investigational Device Exemption (IDE)

An investigational device is a medical device which is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the IDE regulations [21 CFR part 812]. An IDE study may not necessarily commence 30 days after an IDE submission to FDA. Certain clinical investigations of devices (e.g., certain studies of lawfully marketed devices) may be exempt from the IDE regulations [21 CFR 812.2(c)]. Unless exempt from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or "nonsignificant risk" (NSR). The determination that a device presents a nonsignificant or significant risk is initially made by the sponsor. The proposed study is then submitted either to FDA (for SR studies) or to an IRB (for NSR studies).

The IRB's SR/NSR determination has significant consequences for the study sponsor, FDA, and prospective research subjects. SR device studies must be conducted in accordance with the full IDE requirements [21 CFR part 812], and may not commence until 30 days following the sponsor's submission of an IDE application to FDA. Submission of the IDE application enables FDA to review information about the technical characteristics of the device, the results of any prior studies (laboratory, animal and human) involving the device, and the proposed study protocol and consent documents. Based upon the review of this information, FDA may impose restrictions on the study to ensure that risks to subjects are minimized and do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained. The study may not commence until FDA has approved the IDE application and the IRB has approved the study.

In contrast, NSR device studies do not require submission of an IDE application to FDA. Instead, the sponsor is required to conduct the study in accordance with the "abbreviated requirements" of the IDE regulations [21 CFR 812.2(b)]. Unless otherwise notified by FDA, an NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements. The abbreviated requirements address, among other things, the requirements for IRB approval and informed consent, recordkeeping, labeling, promotion, and study monitoring. NSR studies may commence immediately following IRB approval.

IRB Review of the Protocol and Informed Consent

Once the final SR/NSR decision has been rendered by the IRB (or FDA), the IRB must consider whether or not the study should be approved. In considering whether a study should be approved, the IRB should use the same criteria it would use in considering approval of any research involving an FDA regulated product [21 CFR 56.111]. Some NSR studies may also qualify as "minimal risk"

studies, and thus may be reviewed through an expedited review procedure [21 CFR 56.110]. FDA considers all SR studies to present more than minimal risk, and thus, full IRB review is necessary. In making its determination on approval, the IRB should consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures.
Also see these FDA Information Sheets:
"Significant Risk and Nonsignificant Risk Medical Device Studies"
"Sponsor-Investigator-IRB Interrelationship"

Frequently Asked Questions About IRB Review of Medical Devices
5. How does an IRB decide whether a device is SR or NSR?
The IRB uses its best abilities, the information in the regulations and the guidelines, and the risk evaluation provided by the applicant. It can, as always, seek outside assistance. The IRB should have written policies and procedures regarding device review. The information sheet "Significant Risk and Non-Significant Risk Medical Device Studies" provides additional guidance.
6. Does an IRB that reviews medical device studies need written procedures for determining whether the device is SR or NSR?
When the IRB determines that an investigation presented for approval as involving an NSR device actually involves an SR device, 21 CFR 812.66 requires the IRB to so notify the investigator and, where appropriate, the sponsor. 21 CFR 56.108(a)(1) requires the IRB to follow written procedures for conducting its initial review of research and for reporting its findings and actions to the investigator. The procedures followed in determining whether a study is SR or NSR should be included among those written procedures.

Significant Risk and Nonsignificant Risk Medical Device Studies
The Investigational Device Exemption (IDE) regulations [21 CFR part 812] describe two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR). An SR device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations [21

CFR part 56] to identify certain studies that may be approved through an "expedited review" procedure. For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR part 50].

Distinguishing Between SR and NSR Device Studies

The effect of the SR/NSR decision is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations [21 CFR part 812]. NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The major differences are in the approval process and in the record keeping and reporting requirements. The SR/NSR decision is also important to FDA because the IRB serves, in a sense, as the Agency's surrogate with respect to review and approval of NSR studies. FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA. If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA. If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation. To help in the determination of the risk status of the device, IRBs should review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination [21 CFR 812.150(b)(10)].

SR/NSR Studies and the IRB

The NSR/SR Decision

The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor should provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must inform the IRB of the Agency's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the

study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that an SR determination has been made. The study can be conducted as an SR investigation following FDA approval of an IDE application.

The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses an SR, an IRB must consider the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device. Two examples follow:

The study of a pacemaker that is a modification of a commercially--available pacemaker poses a SR because the use of any pacemaker presents a potential for serious harm to the subjects. This is true even though the modified pacemaker may pose less risk, or only slightly greater risk, in comparison to the commercially-available model. The amount of potential reduced or increased risk associated with the investigational pacemaker should only be considered (in relation to possible decreased or increased benefits) when assessing whether the study can be approved.

The study of an extended wear contact lens is considered SR because wearing the lens continuously overnight while sleeping presents a potential for injuries not normally seen with daily wear lenses, which are considered NSR.

FDA has the ultimate decision in determining if a device study is SR or NSR. If the Agency does not agree with an IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the Agency will return the IDE application to the sponsor and the study would be presented to IRBs as an NSR investigation.

IRB and Sponsor Responsibilities Following SR/NSR Determination

If the IRB decides the study is Significant Risk:

1. IRB Responsibilities:

Notify sponsor and investigator of SR decision

After IDE obtained by sponsor, proceed to review study applying requisite criteria [21 CFR 56.111]

2. Sponsor Responsibilities:

Submit IDE to FDA or, if electing not to proceed with study, notify FDA (CDRH Program Operations Staff 301-594-1190) of the SR determination;

Study may not begin until FDA approves IDE and IRB approves the study.

Sponsor and investigator(s) must comply with IDE regulations [21 CFR part 812], as well as informed consent and IRB regulations [21 CFR parts 50 and 56].

If the IRB decides the study is Nonsignificant Risk:

1. IRB proceeds to review study applying requisite criteria [21 CFR 56.111]
2. If the study is approved by the IRB, the sponsor and investigator must comply with "abbreviated IDE requirements" [21 CFR 812.2(b)], and informed consent and IRB regulations [21 CFR parts 50 and 56].

The Decision to Approve or Disapprove

Once the SR/NSR decision has been reached, the IRB should consider whether the study should be approved or not. The criteria for deciding if SR and NSR studies should be approved are the same as for any other FDA regulated study [21 CFR 56.111]. The IRB should assure that risks to subjects are minimized and are reasonable in relation to anticipated benefits and knowledge to be gained, subject selection is equitable, informed consent materials and procedures are adequate, and provisions for monitoring the study and protecting the privacy of subjects are acceptable. To assure that the risks to the subject are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation should be compared to the risks and benefits of alternative devices or procedures. This differs from the judgment about whether a study poses a SR or NSR which is based solely upon the seriousness of the harm that may result from the use of the device. Minutes of IRB meetings must document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

FDA considers studies of all significant risk devices to present more than minimal risk; thus, full IRB review for all studies involving significant risk devices is necessary. Generally, IRB review at a convened meeting is also required when reviewing NSR studies. Some NSR studies, however, may qualify as minimal risk [21 CFR 56.102(i)] and the IRB may choose to review those studies under its expedited review procedures [21 CFR 56.110].

-----Original Message-----
From: [purged]
Sent: Monday, January 19, 2004 6:26 PM
To: GCPQuestions@OC.FDA.GOV
Subject: Question on Investigational Plans/IRBs

Dear FDA,

I teach GCPs/regulations training classes and was recently asked to pinpoint

any regulation that requires submission of the entire Investigational Plan (IP) to the IRB. 21 CFR 56.115(a)(1) (IRB Records) requires, "An...IRB, shall prepare and maintain adequate documentation of IRB acitivities, including the following: (1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals...." The Information Sheets (question 32) state that the IRB should receive and review all research activities...The documents reviewed should include the complete documents received from the clinical investigator, such as the protocol, the investigator's brochure, a sample consent..."

Do these imply that the entire IP must be submitted to the IRB? *or* Does this imply that the IRB does *not* need to be sent the entire investigational plan (including copies of all labeling, detailed device description, IRB information, etc. as outlined in 812.25)? Clearly, the consent materials would have to be submitted, as they are required for appropriate review. I'm in a quandry about this: I don't want to be too conservative, yet I want to communicate a consistent message of compliance to our study teams.

Thanks, as always, for your ever-helpful guidance. And Stan, if you're the person responding, your answer about the use of clinical study worksheets was a great help in guiding our efforts to direct our teams and investigators in proper source documentation practices. Thank you! :-)

Kind regards,
[purged]