

INFORMATION SHEETS

Guidance for Institutional Review Boards and Clinical Investigators 1998 Update

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Sponsor-Investigator-IRB Interrelationship

The interrelationship and interaction between the research sponsor (e.g., drug, biologic and device manufacturers), the clinical investigator and the Institutional Review Board (IRB) may be very complex. The regulations do not prohibit direct sponsor-IRB contacts, although, the sponsor-IRB interaction customarily occurs through the investigator who conducts the clinical study. The clinical investigator generally provides the communication link between the IRB and the sponsor. Such linkage is agreed to by the sponsors and investigators when they sign forms FDA-1571 and FDA-1572, respectively, for drug and biologic studies or an investigator agreement for device studies. There are occasions when direct communication between the IRB and the sponsor may facilitate resolution of concerns about study procedures or specific wording in an informed consent document. The clinical investigator should be kept apprised of the discussion.

Sponsor Assurance that IRBs Operate in Compliance with 21 CFR Part 56

FDA regulations [21 CFR 312.23(a)(1)(iv)] require that a sponsor assure the FDA that a study will be conducted in compliance with the informed consent and IRB regulations [21 CFR parts 50 and 56]. This requirement has been misinterpreted to mean that it is a sponsor's obligation to determine IRB compliance with the regulations. This is not the case. Sponsors should rely on the clinical investigator, who assures the sponsor on form FDA-1572 for drugs and biologics or the investigator agreement for devices that the study will be reviewed by an IRB. Because clinical investigators work directly with IRBs, it is appropriate that they assure the sponsor that the IRB is functioning in compliance with the regulations.

An IRB must notify an investigator in writing of its decision to approve, disapprove or request modifications in a proposed research activity [21 CFR 56.109(e)]. This correspondence should be made available to the sponsor by the clinical investigator. In the Agency's view, this required documentation provides the sponsor with reasonable assurance that an IRB complies with 21 CFR part 56 and that it will be

responsible for initial and continuing review of the study. Also, the sponsor and, in fact, anyone who is interested, may obtain an Establishment Inspection Report from an FDA inspection of an IRB. These reports summarize the conditions observed during the IRB inspection. FDA, however, does not certify IRBs.

Sponsor Access to Medical Records

The IRB is responsible for ensuring that informed consent documents include the extent to which the confidentiality of medical records will be maintained [21 CFR 50.25(a)(5)]. FDA requires sponsors (or research monitors hired by them) to monitor the accuracy of the data submitted to FDA in accordance with regulatory requirements. These data are generally in the possession of the clinical investigator. Each subject must be advised during the informed consent process of the extent to which confidentiality of records identifying the subject will be maintained and of the possibility that the FDA may inspect the records. While FDA access to medical records is a regulatory requirement, subject names are not usually requested by FDA unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual cases studied or actual results obtained. The consent document should list all other entities (e.g., the sponsor) who will have access to records identifying the subject. The extent to which confidentiality will be maintained may affect a subject's decision to participate in a clinical investigation.

Confidentiality of Sponsor Information

The IRB's primary responsibility with respect to protecting confidentiality is to the research subject. IRBs should, however, respect the sponsor's need to maintain confidentiality of certain information about products under development. IRB members and staff should be aware that information submitted for review may be confidential, trade secret, and of commercial interest and should recognize the need for maintaining the confidentiality of the review materials and IRB records. It is advisable for IRBs to have policies that address this issue.

Nonsignificant Risk Device Studies

"A sponsor's preliminary determination that a medical device study presents an NSR is subject to IRB approval." The effect of the IRB's NSR decision is important to research sponsors and investigators because significant risk (SR) studies require sponsors to file an Investigational Device Exemption (IDE) with FDA before they may begin. NSR studies, however, may begin as soon as the IRB approves the study. The sponsor, usually through the clinical investigator, provides the IRB with information necessary to make a judgment on the risk of a device study. While the investigational plan and supporting materials usually contain sufficient information to make a determination, the IRB can request additional information if needed [21 CFR 812.150(b)(10)]. If the IRB believes that additional information is needed, it may contact the sponsor directly, but it should keep the clinical investigator apprised of the request. While making the SR/NSR determination, any of the three parties may ask FDA to provide a risk assessment. See FDA Information Sheet: "Significant Risk and Nonsignificant Risk Medical Device Studies" for further information.

Disagreements

The sponsor may choose not to conduct, to terminate, or to discontinue studies that do not conform with the sponsor's wishes. For example, the sponsor, clinical investigator, and IRB may reach an impasse about study procedures or specific wording in an informed consent document. The FDA will not mediate such disagreements. The Agency's policy of decentralized ethical review of clinical investigations allows such decisions to be made by local IRBs, and any disagreements between a sponsor, IRB, and clinical investigator should be resolved through appropriate communication among those parties.

Acceptance of Foreign Clinical Studies

The Food and Drug Administration (FDA) may accept clinical studies conducted outside the United States in support of safety and efficacy claims for drugs, biological products and medical devices.

All drug, biologic and device studies conducted under an Investigational New Drug (IND) or Investigational Device Exemption (IDE) are governed by the FDA informed consent and IRB requirements. [See 21 CFR part 312 IND regulations and 21 CFR part 812 IDE regulations.]

Under 21 CFR 312.120(c)(1), FDA will accept a foreign clinical study involving a drug or biological product not conducted under an IND only if the study conforms to whichever of the following provides greater protection of the human subjects:

- the ethical principles contained in the 1989 version of the Declaration of Helsinki, or
- the laws and regulations of the country in which the research was conducted.

Under 21 CFR 814.15(a) and (b), FDA will accept a foreign clinical study involving a medical device not conducted under an IDE only if the study conforms to whichever of the following provides greater protection of the human subjects:

- the ethical principles contained in the 1983 version of the Declaration of Helsinki, or
- the laws and regulations of the country in which the research was conducted.

Also see these FDA Information Sheets:

["Non-Local IRB Review"](#)

["Waiver of IRB Requirements for Drug and Biologic Studies"](#)

"Informed Consent and the Clinical Investigator"

Declaration of Helsinki--the [1983](#) and [1989](#) versions

Charging for Investigational Products

This information sheet discusses FDA policy on allowing charges for the test articles in clinical investigations.

Decisions concerning charging subjects for investigational products are guided by professional ethics, institutional policies, and FDA regulations. The FDA informed consent regulations require the consent document to include a description of any additional costs to the subject that may result from participation in the research [21 CFR 50.25(b)(3)]. IRBs should ensure that the informed consent documents outline any additional costs that will be billed to study subjects or their insurance company as a result of participation in the study. IRBs should also ensure that any such charges are appropriate and equitable.

Because the regulations governing drugs and biologics vary from those governing medical devices, the Agency's position on charging for the test articles will be discussed separately. FDA does not prohibit charging the subjects for related treatment or for services.

1. Charging for Investigational Medical Devices and Radiological Health Products

The Investigational Device Exemption (IDE) regulations allow sponsors to charge for an investigational device, however, the charge should not exceed an amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device [21 CFR 812.7(b)]. A sponsor justifies the proposed charges for the device in the IDE application, states the amount to be charged, and explains why the charge does not constitute commercialization [21 CFR 812.20(b)(8)]. FDA generally allows sponsors to charge investigators for investigational devices, and this cost usually is passed on to the subjects.

2. Charging for Investigational Drugs and Biologics

The Investigational New Drug (IND) regulations [21 CFR 312.7(d)] permit a sponsor to charge for an investigational drug or biologic that has not been approved for marketing, only under the conditions outlined below. In both a clinical trial and a treatment IND, the charge should not exceed an amount that is necessary to recover the costs associated with the manufacture, research, development, and handling of the investigational drug or biologic. FDA may withdraw authorization to charge if the Agency finds that the conditions underlying the authorization are no longer satisfied.

(i) Clinical Trials Under an IND

A sponsor may not charge for an investigational drug or biologic in a clinical trial under an IND without the Agency's prior written approval. In requesting such approval, the sponsor must explain why a charge is necessary, i.e., why providing the product

without charge should not be considered part of the normal cost of conducting a clinical trial [21 CFR 312.7(d)(1)].

(ii) Treatment Protocol or Treatment IND

A sponsor or investigator may charge for an investigational drug or biologic for a treatment use under a treatment protocol or treatment IND, as outlined in 21 CFR 312.34 and 312.35, provided: (1) there is adequate enrollment in the ongoing clinical investigations under the authorized IND; (2) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (3) the drug or biologic is not being commercially promoted or advertised; and (4) the sponsor is actively pursuing marketing approval with due diligence. FDA must be notified in writing prior to commencing any such charges. Authorization for charging goes into effect automatically 30 days after receipt of the information by FDA, unless FDA notifies the sponsor to the contrary [21 CFR 312.7(d)(2)].

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.

Recruiting Study Subjects

FDA requires that an Institutional Review Board (IRB) review and have authority to approve, require modifications in, or disapprove all research activities covered by the IRB regulations [21 CFR 56.109(a)]. An IRB is required to ensure that appropriate safeguards exist to protect the rights and welfare of research subjects [21 CFR 56.107(a) and 56.111]. In fulfilling these responsibilities, an IRB is expected to review all the research documents and activities that bear directly on the rights and welfare of the subjects of proposed research. The protocol, the consent document and, for studies conducted under the Investigational New Drug (IND) regulations, the investigator's brochure are examples of documents that the IRB should review. The IRB should also review the methods and material that investigators propose to use to recruit subjects.

A. Media Advertising:

Direct advertising for research subjects, i.e., advertising that is intended to be seen or heard by prospective subjects to solicit their participation in a study, is not in and of itself, an objectionable practice. Direct advertising includes, but is not necessarily limited to: newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects. **Not included** are: (1) communications intended to be seen or heard by health professionals, such as "dear doctor" letters and doctor-to-doctor letters (even when soliciting for study subjects), (2) news stories and (3) publicity intended for other audiences, such as financial page advertisements directed toward prospective investors.

IRB review and approval of listings of clinical trials on the internet would provide no additional safeguard and is not required when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information. Examples of clinical trial listing services that do not require prospective IRB approval include the National Cancer Institute's cancer clinical trial listing (PDQ) and the government-sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information is not precluded by the data base system, IRB review and approval may assure that the additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process. Advertisements should be reviewed and approved by the IRB as part of the package for initial review. However, when the clinical investigator decides at a later date to advertise for subjects, the advertising may be considered an amendment to the ongoing study. When such advertisements are easily compared to the approved consent document, the IRB chair, or other designated IRB member, may review and approve by expedited means, as provided by 21 CFR 56.110(b)(2). When the IRB reviewer has doubts or other complicating issues are involved, the advertising should be reviewed at a convened meeting of the IRB.

FDA expects IRBs to review the advertising to assure that it is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence. [21 CFR 50.20, 50.25, 56.111(a)(3), 56.111(b) and 812.20(b)(11).]

When direct advertising is to be used, the IRB should review the information contained in the advertisement and the mode of its communication, to determine that the procedure for recruiting subjects is not coercive and does not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol. The IRB should review the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. When advertisements are to be taped for broadcast, the IRB should review the final audio/video tape. The IRB may review and approve the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording. The review of the final taped message prepared from IRB-approved text may be accomplished through expedited procedures. The IRB may wish to caution the clinical investigators to obtain IRB approval of message text prior to taping, in order to avoid re-taping because of inappropriate wording.

No claims should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device. Such representation would not only be misleading to subjects but would also be a violation of the Agency's regulations concerning the promotion of investigational drugs [21 CFR 312.7(a)] and of investigational devices [21 CFR 812.7(d)].

Advertising for recruitment into investigational drug, biologic or device studies should not use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational. A phrase such as "receive new treatments" leads study subjects to believe they will be receiving newly improved products of proven worth.

Advertisements should not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation. Advertisements may state that subjects will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type.

Generally, FDA believes that any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements. It should be noted, however, that FDA does not require inclusion of all of the listed items.

1. the name and address of the clinical investigator and/or research facility;
2. the condition under study and/or the purpose of the research;
3. in summary form, the criteria that will be used to determine eligibility for the study;
4. a brief list of participation benefits, if any (e.g., a no-cost health examination);
5. the time or other commitment required of the subjects; and
6. the location of the research and the person or office to contact for further information.

B. Receptionist Scripts.

The first contact prospective study subjects make is often with a receptionist who follows a script to determine basic eligibility for the specific study. The IRB should assure the procedures followed adequately protect the rights and welfare of the prospective subjects. In some cases personal and sensitive information is gathered about the individual. The IRB should have assurance that the information will be appropriately handled. A simple statement such as "confidentiality will be maintained" does not adequately inform the IRB of the procedures that will be used.

Examples of issues that are appropriate for IRB review: What happens to personal information if the caller ends the interview or simply hangs up? Are the data gathered by a marketing company? If so, are names, etc. sold to others? Are names of non-eligibles maintained in case they would qualify for another study? Are paper copies of records shredded or are readable copies put out as trash? The acceptability of the procedures would depend on the sensitivity of the data gathered, including; personal, medical and financial.

Also see these FDA Information Sheets:
["A Guide to Informed Consent Documents"](#)
["Payment to Research Subjects"](#)

Payment to Research Subjects

The Institutional Review Board (IRB) should determine that the risks to subjects are reasonable in relation to anticipated benefits [21 CFR 56.111(a)(2)] and that the consent document contains an adequate description of the study procedures [21 CFR 50.25(a)(1)] as well as the risks [21 CFR 50.25(a)(2)] and benefits [21 CFR 50.25(a)(3)]. It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic or device development. Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive. Financial incentives are often used when health benefits to subjects are remote or non-existent. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20].

Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to subjects who had withdrawn before that date.

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Also see these FDA Information Sheets:
["A Guide to Informed Consent Documents"](#)
["Recruiting Study Subjects."](#)

Screening Tests Prior to Study Enrollment

For some studies, the use of screening tests to assess whether prospective subjects are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. While an investigator may discuss availability of studies and the possibility of entry into a study with a prospective subject without first obtaining consent, informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from medication (wash-out). When wash-out is done in anticipation of or in preparation for the research, it is part of the research.

Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any clinical screening procedures that is performed solely for the purpose of determining eligibility for research. When a doctor-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility for research enrollment are not required for their medical care. Physician-investigators should take extra care to clarify with their patient-subjects why certain tests are being conducted.

Clinical screening procedures for research eligibility are considered part of the subject selection and recruitment process and, therefore, require IRB oversight. If the screening qualifies as a minimal risk procedure [21 CFR 56.102(i)], the IRB may choose to use expedited review procedures [21 CFR 56.110]. The IRB should receive a written outline of the screening procedure to be followed and how consent for screening will be obtained. The IRB may find it appropriate to limit the scope of the screening consent to a description of the screening tests and to the reasons for performing the tests including a brief summary description of the study in which they may be asked to participate. Unless the screening tests involve more than minimal risk or involve a procedure for which written consent is normally required outside the research context, the IRB may decide that prospective study subjects need not sign a consent document [21 CFR 56.109(c)]. If the screening indicates that the prospective subject is eligible, the informed consent procedures for the study, as approved by the IRB, would then be followed.

Certain clinical tests, such as for HIV infection, may have State requirements regarding (1) the information that must be provided to the participant, (2) which organizations have access to the test results and (3) whether a positive result has to be reported to the health department. Prospective subjects should be informed of any such requirements and how an unfavorable test result could affect employment or insurance before the test is conducted. The IRB may wish to confirm that such tests are required by the protocol of the study.

Also see this FDA Information Sheet:
["Recruiting Study Subjects"](#)