Contains Nonbinding Recommendations

Guidance for Clinical Investigators, Institutional Review Boards and Sponsors

Process for Handling Referrals to FDA Under 21 CFR 50.54

Additional Safeguards for Children in Clinical Investigations

DRAFT GUIDANCE

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For single copies of this draft guidance, please contact: Office of Policy, Food and Drug Administration, 5600 Fishers Lane, rm. 14-101, HF-11, Rockville, MD 20857, (301) 827-3360.

For questions regarding this draft document, contact Erik Mettler, Office of Policy, (301) 827-3360.

U.S. Department of Health and Human Services
Food and Drug Administration
May 2006

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Draft Guidance

Table of Contents

GUIDANCE FOR CLINICAL INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS AND SPONSORS

Process for Handling Referrals to FDA Under 21 CFR 50.54 Additional Safeguards for Children in Clinical Investigations

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist clinical investigators, Institutional Review Boards (IRBs), sponsors, and other interested parties in understanding the Food and Drug Administration's (FDA or agency) process for handling clinical investigations that include children as subjects and that have been referred to FDA for review under 21 CFR 50.54. This guidance describes the procedures FDA generally intends to follow in handling such clinical investigations and in reaching final determinations pursuant to that regulation. It is based in part on FDA's experience to date with such referrals. The Department of Health and Human Services (HHS) has human subject protection regulations that also govern research involving children and supported or conducted by HHS. (See 45 CFR Part 46 Subpart D.) This guidance also addresses situations in which a clinical investigation is subject to both 21 CFR 50.54 and 45 CFR 46.407.[1]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should *in FDA's guidances means that something is suggested or recommended, but not required.*

II. BACKGROUND

FDA adopted 21 CFR Part 50 Subpart D, "Additional Safeguards for Children in Clinical Investigations", as an interim final rule in April 2001 (21 CFR Part 50, Subpart D) (Subpart D)

[1] The HHS Subpart D regulations are implemented and interpreted by HHS's Office for Human Research Protections (OHRP) and are nearly identical to FDA's regulations. OHRP has posted on its website information pertaining to its process for handling clinical protocols that are subject to 45 CFR 46.407, and to 45 CFR 46.407 as well as FDA's Subpart D regulations. See www.hhs.gov/ohrp/children/guidance_407process.html.

(See 66 FR 20598, April 24, 2001). Under these regulations an IRB must review clinical investigations that involve children as subjects and are covered by Subpart D and must approve only those clinical investigations that satisfy the criteria described in 21 CFR 50.51, 50.52 or 50.53, and the conditions of all other applicable sections of Subpart D. If an IRB does not believe that a clinical investigation within the scope described in 21 CFR 50.1 and 56.101 and involving children as subjects meets the requirements of 21 CFR 50.51, 50.52 or 50.53, the clinical investigation may proceed only if:

- The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
- The Commissioner of Food and Drugs (Commissioner), after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:
  - -The clinical investigation in fact satisfies 21 CFR 50.51, 50.52 or 50.53, or
  - -The following three conditions described in 21 CFR 50.54 are met:
    1. The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
    2. The clinical investigation will be conducted in accordance with sound ethical principles; and
    3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in §50.55.

III. REVIEW PROCESS

In FDA-regulated clinical investigations involving children, the agency makes every effort to protect the rights, safety, and welfare of those children. In addition, the agency strives to achieve the basic goals of adherence to sound ethical principles, transparency through public and expert input, efficiency, timeliness, clarity, and consistency. These goals are also endorsed by the Subcommittee on Research Involving Children of the Secretary's Advisory Committee on Human Research Protections (SACHRP).[2] FDA believes that these goals are best served by having a clear, efficient, and comprehensive process for referrals by IRBs under 21 CFR 50.54.

A. Overview of Process

FDA will use its advisory committee process to evaluate clinical investigations referred for review under 21 CFR 50.54. This process will provide transparency and help ensure expert input as well as public participation. When FDA receives a referral from an IRB, the agency will determine if the clinical investigation described in the protocol is regulated by FDA as described in 21 CFR 50.1(a). If so, the agency will determine whether the referral is complete and can be accepted for processing. If the referral is accepted, the agency generally will call a meeting of the Pediatric Ethics Subcommittee (the Subcommittee) of the Pediatric Advisory Committee

[2] See Recommendations for OHRP/FDA Harmonization Subcommittee on Research Involving Children of SACHRP, January 29, 2004 minutes, page 9.

(PAC) and present the referral to the Subcommittee for its consideration. At the next open meeting of the PAC, the Subcommittee chair (or another member of the Subcommittee, if the chair is unavailable) will present to the PAC the Subcommittee's recommendation(s) regarding the referred clinical investigation. After discussion and deliberation, the PAC will make its recommendation(s) regarding the referral to the Commissioner of Food and Drugs. The Commissioner will then make the final determination as to whether the clinical investigation meets the requirements of FDA's Subpart D regulations. This process is discussed in greater detail below.

B. Public Participation

Public review and comment is required under 21 CFR 50.54. Furthermore, FDA believes that public participation is important to help ensure the comprehensiveness and integrity of the review of clinical investigations referred under that regulation and the protection of the children who may be enrolled in the investigations. In order to encourage public participation, FDA intends to establish an agency docket for each accepted referral and solicit public comment on the proposed investigation. The materials in the docket for each investigation will include the referral documents sent by the IRB, related agency correspondence, public comments on the referral, the transcripts of both the Subcommittee meeting and the PAC meeting, and the final determination of the Commissioner regarding the referral under 21 CR 50.54. Materials submitted to the docket will be available through FDA's Division of Dockets Management or through FDA's Freedom of Information Act office.

In addition, the Subcommittee and PAC meetings will be open to the public At the Subcommittee meeting, the chair will also present a summary of the public comments received.

C. The Subcommittee and Advisory Committee Meetings

When FDA receives an appropriate and complete[3] referral from an IRB under 21 CFR 50.54, the Office of Pediatric Therapeutics (OPT) will coordinate with the Executive Secretary of the PAC regarding the scheduling of the Subcommittee and PAC meetings. FDA generally expects to schedule Subcommittee meetings directly preceding a scheduled PAC meeting. The PAC is currently scheduled to meet approximately three times per year.

FDA intends to invite a representative of the referring IRB (to be selected by the IRB) and the principal investigator to attend the Subcommittee meeting and to make a presentation to the Subcommittee regarding the referred protocol. The agency encourages the IRB representative and the principal investigator to attend the meeting to help the Subcommittee understand the clinical investigation and basis for the referral. One or more representatives from the FDA review division responsible for reviewing the clinical investigation may also attend to answer questions from the Subcommittee. Although a referral may be made because of a particular aspect of the clinical investigation, the Subcommittee and the PAC, as well as FDA (and OHRP if they are involved[4]), usually will consider the clinical investigation in its entirety.

[3] See discussion of a complete referral below in section III.E.

[4] See discussion of the joint review process with OHRP in section III.O

At the next PAC meeting following the Subcommittee meeting, the Subcommittee chair (or another member of the Subcommittee, if the chair is unavailable) will present the Subcommittee's recommendation(s) regarding whether the clinical investigation meets the requirements of Subpart D and other relevant requirements of Part 50. The PAC can accept the Subcommittee's recommendations as presented, accept them with changes, or formulate its own. The recommendations may include changes that the PAC believes are necessary for the clinical investigation to proceed as well as other suggested changes to improve the investigation. OPT will forward all of the recommendations of the PAC and the Subcommittee, along with any additional recommendations/comments from OPT, to the Commissioner. In cases where FDA and OHRP are working jointly to review a clinical investigation subject to both FDA's and HHS' regulations, the PAC recommendation(s) also will be made to the Secretary.

Both the Subcommittee and the PAC will operate by majority vote.

D. Submitting a Referral

IRBs should send referrals under 21 CFR 50.54 of clinical investigations regulated by FDA, as described in 21 CFR 50.1(a), to FDA's OPT at opt@fda.gov, or Office of Pediatric Therapeutics, Office of the Commissioner, FDA, 5600 Fishers Lane, RM 13B-45, HFG-2, Rockville, MD 20857. FDA may also receive copies of referrals from OHRP in situations where an IRB has referred a clinical investigation to OHRP but not to FDA. Similarly, if an IRB submits a clinical investigation to FDA but not to OHRP, FDA will usually send it to OHRP so that OHRP can determine whether the clinical investigation is also subject to HHS jurisdiction. If a clinical investigation is subject to both HHS and FDA jurisdiction, then, as discussed below in Section III.O, the referral process will be conducted jointly by FDA and OHRP under 21 CFR 50.54 and 45 CFR 46.407.

E. Documents to Include in the Referral

If an IRB decides to refer a clinical investigation for consideration under 21 CFR 50.54, the IRB should submit its finding (required under 21 CFR 50.54(a)) that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. The IRB should refer to 21 CFR 56.115 to be sure that all required documents to support this finding have been supplied.

The referral should also include the following:

- An explanation as to why the IRB does not believe that the clinical investigation meets the requirements of 21 CFR 50.51, 50.52, or 50.53. FDA believes that in most cases this probably will be explained in the IRB's minutes from its discussions of the protocol at issue.
- The research protocol and, if the clinical investigation is being conducted under an Investigational New Drug application (IND) or Investigational Device Exemption (IDE), the IND or IDE number assigned by FDA;
- All informed consent documents, including the parental permission form and, if being used, the assent forms and/or a description of the assent process; and

- Any other informative supporting documents, such as IRB minutes pertinent to the clinical investigation, correspondence between the IRB and the principal investigator, product labeling, and the investigator's brochures.

In addition, the IRB should ensure that the submitted documents consistently describe the clinical investigation**. Electronic versions of all documents are strongly encouraged.**

These documents are needed to allow FDA to complete its initial assessment of the clinical investigation to determine if the study is subject to FDA jurisdiction, and to provide the Subcommittee and the PAC with complete information regarding the referral. The referring IRB should provide these additional documents in a form the IRB would find approvable, but for the issue(s) that prompted the referral under 21 CFR 50.54. Providing these additional documents in "IRB-approvable" condition will allow the Subcommittee and the PAC to focus on the issue(s) that prompted the referral, and not on other matters that the IRB is able to resolve itself.

When OPT receives a referral, it will contact the referring IRB to confirm receipt of the referral. This will begin the process of exchanging information about the clinical investigation between OPT, the IRB, and the principal investigator. Either in that initial contact or subsequently, OPT will advise the IRB as to whether the clinical investigation is subject to FDA jurisdiction and, if it is, whether the referral is complete, and thus acceptable for review, or whether any information is missing from the submission. Depending on the circumstances of the research, OPT may ask for additional information, which may include, for example, information regarding the past use of the investigational article in children or adults, documents regarding continuing review, the IND/IDE status, drug preparation protocol, or the certificate of analysis for the chemical being studied. During this exchange OPT will explain the procedures the agency intends to follow and will encourage the IRB to ask any questions it might have about the requirements of 21 CFR 50.54.

Following this exchange, the IRB may decide that it wishes to withdraw the referral from consideration. The reasons for withdrawal could include, for example, a misunderstanding of the requirements of the Subpart D regulations and the applicability of 50.54 to the clinical investigation at issue, i.e., a determination by the IRB after further analysis that the clinical investigation can in fact proceed under another provision in the Subpart D regulations. Withdrawal of a referral under circumstances such as these would be understandable and would avoid the unnecessary expenditure of agency and IRB resources. FDA suggests that an IRB in doubt about whether to refer a clinical investigation under 50.54 consult with OPT as soon as possible via email at opt@fda.gov.

F. Assessment of Referral

Following receipt of the referral, FDA will determine whether the protocol is FDA-regulated (generally within 2 weeks after receipt) and inform the referring IRB in writing of the determination. If the clinical investigation was referred to FDA by OHRP, FDA will also inform OHRP of that determination.

The considerations under FDA's IND regulations (see 21 CFR Part 312) and IDE regulations (see 21 CFR Part 812) that are used to determine whether an IND or IDE can go into effect are related to, but distinct from, the considerations under Part 50 regarding the protection of human subjects. Therefore, IRBs should note that, although some clinical investigations are exempt from the need to be conducted under an IND (see 21 CFR 312.2(b)), those that are exempt are still subject to 21 CFR Parts 50 and 56 and thus may trigger the Subpart D process under section 50.54. Similarly, a clinical investigation of a medical device may be exempt under 21 CFR 812.2(c) from the requirement that it be conducted under an IDE, but the clinical investigation may still be subject to the Subpart D process. Furthermore, as indicated in 21 CFR 50.1(a), Part 50 also applies to certain investigations that are not subject to sections 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act (21 USC §§ 355(i), 360j(g)).

G. Acceptance of Referral

Following receipt of the referral, OPT will then ask the referring IRB for any other relevant documents and inform the IRB that FDA intends to post the documents in the docket created for the referral, and on the agency's website. If the IRB believes that any documents it has included in its referral may be considered confidential by the sponsor, the IRB will be responsible for obtaining any necessary permission from the sponsor to post the documents. If an IRB (or sponsor) objects to the public posting of the documents, the agency will be unable to proceed with the referral.

H. Multi-Site Clinical Investigations

In some circumstances clinical investigations referred for review under 21 CFR 50.54 may be conducted at multiple sites. In the event that an IRB at one or more of the clinical sites refers the investigation for review, it should notify the sponsor. In such a situation, FDA strongly encourages the sponsor to notify the IRB(s) and principal investigator(s) at all of the other sites of the referral. Once an IRB has made a referral under 50.54, pursuant to that regulation the investigation may not proceed (i.e., no subjects should be recruited or enrolled in the investigation) at any site for which that IRB has responsibility.

IRBs at other clinical sites may wish to allow the investigation to proceed despite being notified of the referral; IRBs at other sites should consider the implications of continuing the investigation during the pendency of the review and determination under 21 CFR 50.54. For example, at the conclusion of the review, it is possible that the Commissioner could determine that the investigation cannot proceed because one or more of the criteria in 21 CFR 50.54(b) are not met. Alternatively, the Commissioner might determine that the investigation can proceed but only with modifications of the protocol or the informed consent documents and procedures.

I. Draft of Federal Register Notices

Following a referral, FDA generally will issue three Federal Register notices:

- A solicitation of public comments on the referral, along with background information for the referral, notice of the establishment of a docket for the referral, and directions for how

to access the docket. Generally, FDA will provide approximately 4 weeks for submission of comments to the docket;

- The announcement of the Pediatric Ethics Subcommittee meeting; and
- The announcement of the Pediatric Advisory Committee meeting.

J. Composition of the Pediatric Ethics Subcommittee

FDA will select the members of the Subcommittee in accordance with 21 CFR 50.54(b) and other relevant federal laws, including the Federal Advisory Committee Act (FACA) (5 U.S.C. App. 2)(1972). The Subcommittee will include at least two members of the PAC. FDA will also invite individuals to serve on the Subcommittee who have expertise and/or experience relevant to the clinical investigation being discussed. As a general matter, OPT will make these selections in collaboration with the relevant FDA Center(s) and review division(s). Additional individuals will be invited according to the principles set forth in 21 CFR 50.54(b), such that the Subcommittee consists of a "panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law)" (21 CFR 50.54(b)). As a general matter, FDA also believes that usually it will be helpful to include a patient advocate/community representative and a statistician on the Subcommittee.

The agency notes that there will be no cap on the number of members of the Subcommittee, and the agency will include as many members as necessary to ensure that the relevant expertise is represented.

K. The Subcommittee Meeting

FDA anticipates that a Subcommittee meeting usually will last for one day and a typical agenda will include:

- Call to order
- Meeting statement
- Description of Subpart D expert panel process
- Overview, charge to panel
- Background of clinical investigation and protocol-specific scientific/medical issues
- Principal investigator comments
- IRB comments, including identification of specific ethical issues which led to the referral
- Summary of public comments
- Open public hearing
- Presentation of questions
- Expert panel discussion
- Discussion, agreement, and vote on recommendation(s) (summary of deliberations) that will be presented to PAC.

Meeting transcripts and recommendations from the Subcommittee meeting will be made available to the public in the docket established for the referral and on the agency's website.

L. PAC Meeting

At the next meeting of the PAC (usually shortly after the Subcommittee meeting), the chair of the Subcommittee (or another member of the Subcommittee, if the chair is unavailable) will present a summary of its deliberations and recommendation(s) to the PAC for discussion. After discussion of the recommendation(s) and the clinical investigation itself, the PAC will vote on its recommendation(s) to the Commissioner regarding whether the proposed clinical investigation may proceed under 21 CFR Part 50 Subpart D. Meeting transcripts and recommendation(s) from the PAC meeting will be made available to the public in the docket established for the referral and on the agency's website. After the PAC meeting, the chair will usually summarize the recommendation(s) of the PAC in a letter to OPT.

M. Transmittal Memorandum

OPT will draft and send a transmittal memorandum to the Commissioner outlining the PAC and PES recommendation(s), and including any additional recommendations/comments that OPT may have. The transmittal memorandum also will include any other necessary supporting documentation. The transmittal memorandum will request that the Commissioner make a final determination as to whether, and if so, under what provisions of Subpart D, the clinical investigation may proceed. After the Commissioner has made a final determination, OPT will forward that determination to the referring IRB and will post it in the docket created for the referral and on the agency's website.

N. Referral Process Timing

OPT projects that this referral process will take approximately six months to complete; complex submissions may take longer to process (e.g., protocols involving a joint referral with OHRP).

O. FDA-DHHS joint review under 21 CFR 50.54 and 45 CFR 46.407

In light of the need for both consistency and expediency, the process for IRB referrals of proposed clinical investigations that are both HHS-conducted or supported and FDA-regulated will function in essentially the same manner as the process for FDA-only referrals. In such cases:

- HHS, through OHRP, will participate in the selection of members for the Subcommittee.
- After the Subcommittee makes a recommendation to the PAC, the PAC will make its recommendation(s) to both the Secretary of HHS and the Commissioner of Food and Drugs.
- OPT will forward the Commissioner's determination to OHRP.
- OHRP will send a transmittal memo with its recommendation, the Commissioner's determination, and all supporting documents, including the recommendation(s) of the PAC and the summary of the Subcommittee meeting, to the Secretary for a determination as to whether the clinical investigation may be conducted or supported by HHS.