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# **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### **DRAFT GUIDANCE**

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For single copies of this draft guidance, please contact: Office of Policy, Food and Drug Administration, 5600 Fishers Lane, rm. 14-101, HF-11, Rockville, MD 20857, (301) 827-3360.

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

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**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**

Additional copies are available from:  
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**U.S. Department of Health and Human Services  
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7

8 *This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s)*  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

14  
15  
16 **I. INTRODUCTION**  
17

18 This guidance is intended to assist clinical investigators, Institutional Review Boards (IRBs),  
19 sponsors, and other interested parties in understanding the Food and Drug Administration’s  
20 (FDA or agency) process for handling clinical investigations that include children as subjects and  
21 that have been referred to FDA for review under 21 CFR 50.54. This guidance describes the  
22 procedures FDA generally intends to follow in handling such clinical investigations and in  
23 reaching final determinations pursuant to that regulation. It is based in part on FDA’s experience  
24 to date with such referrals. The Department of Health and Human Services (HHS) has human  
25 subject protection regulations that also govern research involving children and supported or  
26 conducted by HHS. (See 45 CFR Part 46 Subpart D.) This guidance also addresses situations in  
27 which a clinical investigation is subject to both 21 CFR 50.54 and 45 CFR 46.407.<sup>1</sup>  
28

29 *FDA’s guidance documents, including this guidance, do not establish legally enforceable*  
30 *responsibilities. Instead, guidances describe the FDA’s current thinking on a topic and should*  
31 *be viewed only as recommendations, unless specific regulatory or statutory requirements are*  
32 *cited. The use of the word should in FDA’s guidances means that something is suggested or*  
33 *recommended, but not required.*  
34  
35

36 **II. BACKGROUND**  
37

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

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<sup>1</sup> 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](http://www.hhs.gov/ohrp/children/guidance_407process.html).

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40 (See 66 FR 20598, April 24, 2001). Under these regulations an IRB must review clinical  
41 investigations that involve children as subjects and are covered by Subpart D and must approve  
42 only those clinical investigations that satisfy the criteria described in 21 CFR 50.51, 50.52 or  
43 50.53, and the conditions of all other applicable sections of Subpart D. If an IRB does not  
44 believe that a clinical investigation within the scope described in 21 CFR 50.1 and 56.101 and  
45 involving children as subjects meets the requirements of 21 CFR 50.51, 50.52 or 50.53, the  
46 clinical investigation may proceed only if:

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

### 64 **III. REVIEW PROCESS**

65  
66 In FDA-regulated clinical investigations involving children, the agency makes every effort to  
67 protect the rights, safety, and welfare of those children. In addition, the agency strives to achieve  
68 the basic goals of adherence to sound ethical principles, transparency through public and expert  
69 input, efficiency, timeliness, clarity, and consistency. These goals are also endorsed by the  
70 Subcommittee on Research Involving Children of the Secretary's Advisory Committee on  
71 Human Research Protections (SACHRP).<sup>2</sup> FDA believes that these goals are best served by  
72 having a clear, efficient, and comprehensive process for referrals by IRBs under 21 CFR 50.54.

#### 74 **A. Overview of Process**

75  
76 FDA will use its advisory committee process to evaluate clinical investigations referred for  
77 review under 21 CFR 50.54. This process will provide transparency and help ensure expert input  
78 as well as public participation. When FDA receives a referral from an IRB, the agency will  
79 determine if the clinical investigation described in the protocol is regulated by FDA as described  
80 in 21 CFR 50.1(a). If so, the agency will determine whether the referral is complete and can be  
81 accepted for processing. If the referral is accepted, the agency generally will call a meeting of  
82 the Pediatric Ethics Subcommittee (the Subcommittee) of the Pediatric Advisory Committee

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

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

### **B. Public Participation**

91  
92  
93  
94 Public review and comment is required under 21 CFR 50.54. Furthermore, FDA believes that  
95 public participation is important to help ensure the comprehensiveness and integrity of the  
96 review of clinical investigations referred under that regulation and the protection of the children  
97 who may be enrolled in the investigations. In order to encourage public participation, FDA  
98 intends to establish an agency docket for each accepted referral and solicit public comment on  
99 the proposed investigation. The materials in the docket for each investigation will include the  
100 referral documents sent by the IRB, related agency correspondence, public comments on the  
101 referral, the transcripts of both the Subcommittee meeting and the PAC meeting, and the final  
102 determination of the Commissioner regarding the referral under 21 CR 50.54. Materials  
103 submitted to the docket will be available through FDA's Division of Dockets Management or  
104 through FDA's Freedom of Information Act office.

105  
106 In addition, the Subcommittee and PAC meetings will be open to the public. At the  
107 Subcommittee meeting, the chair will also present a summary of the public comments received.

### **C. The Subcommittee and Advisory Committee Meetings**

108  
109  
110  
111 When FDA receives an appropriate and complete<sup>3</sup> referral from an IRB under 21 CFR 50.54, the  
112 Office of Pediatric Therapeutics (OPT) will coordinate with the Executive Secretary of the PAC  
113 regarding the scheduling of the Subcommittee and PAC meetings. FDA generally expects to  
114 schedule Subcommittee meetings directly preceding a scheduled PAC meeting. The PAC is  
115 currently scheduled to meet approximately three times per year.

116  
117 FDA intends to invite a representative of the referring IRB (to be selected by the IRB) and the  
118 principal investigator to attend the Subcommittee meeting and to make a presentation to the  
119 Subcommittee regarding the referred protocol. The agency encourages the IRB representative  
120 and the principal investigator to attend the meeting to help the Subcommittee understand the  
121 clinical investigation and basis for the referral. One or more representatives from the FDA  
122 review division responsible for reviewing the clinical investigation may also attend to answer  
123 questions from the Subcommittee. Although a referral may be made because of a particular  
124 aspect of the clinical investigation, the Subcommittee and the PAC, as well as FDA (and OHRP  
125 if they are involved<sup>4</sup>), usually will consider the clinical investigation in its entirety.

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<sup>3</sup> See discussion of a complete referral below in section III.E.

<sup>4</sup> See discussion of the joint review process with OHRP in section III.O

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

138  
139 Both the Subcommittee and the PAC will operate by majority vote.

140

### **D. Submitting a Referral**

141

142  
143 IRBs should send referrals under 21 CFR 50.54 of clinical investigations regulated by FDA, as  
144 described in 21 CFR 50.1(a), to FDA's OPT at opt@fda.gov, or Office of Pediatric Therapeutics,  
145 Office of the Commissioner, FDA, 5600 Fishers Lane, RM 13B-45, HFG-2, Rockville, MD  
146 20857. FDA may also receive copies of referrals from OHRP in situations where an IRB has  
147 referred a clinical investigation to OHRP but not to FDA. Similarly, if an IRB submits a clinical  
148 investigation to FDA but not to OHRP, FDA will usually send it to OHRP so that OHRP can  
149 determine whether the clinical investigation is also subject to HHS jurisdiction. If a clinical  
150 investigation is subject to both HHS and FDA jurisdiction, then, as discussed below in Section  
151 III.O, the referral process will be conducted jointly by FDA and OHRP under 21 CFR 50.54 and  
152 45 CFR 46.407.

153

### **E. Documents to Include in the Referral**

154

155  
156 If an IRB decides to refer a clinical investigation for consideration under 21 CFR 50.54, the IRB  
157 should submit its finding (required under 21 CFR 50.54(a)) that the clinical investigation  
158 presents a reasonable opportunity to further the understanding, prevention, or alleviation of a  
159 serious problem affecting the health or welfare of children. The IRB should refer to 21 CFR  
160 56.115 to be sure that all required documents to support this finding have been supplied.

161

162 The referral should also include the following:

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

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- 172       • Any other informative supporting documents, such as IRB minutes pertinent to the  
173       clinical investigation, correspondence between the IRB and the principal investigator,  
174       product labeling, and the investigator's brochures.  
175

176 In addition, the IRB should ensure that the submitted documents consistently describe the  
177 clinical investigation. **Electronic versions of all documents are strongly encouraged.**  
178

179 These documents are needed to allow FDA to complete its initial assessment of the clinical  
180 investigation to determine if the study is subject to FDA jurisdiction, and to provide the  
181 Subcommittee and the PAC with complete information regarding the referral. The referring IRB  
182 should provide these additional documents in a form the IRB would find approvable, but for the  
183 issue(s) that prompted the referral under 21 CFR 50.54. Providing these additional documents in  
184 "IRB-approvable" condition will allow the Subcommittee and the PAC to focus on the issue(s)  
185 that prompted the referral, and not on other matters that the IRB is able to resolve itself.  
186

187 When OPT receives a referral, it will contact the referring IRB to confirm receipt of the referral.  
188 This will begin the process of exchanging information about the clinical investigation between  
189 OPT, the IRB, and the principal investigator. Either in that initial contact or subsequently, OPT  
190 will advise the IRB as to whether the clinical investigation is subject to FDA jurisdiction and, if  
191 it is, whether the referral is complete, and thus acceptable for review, or whether any information  
192 is missing from the submission. Depending on the circumstances of the research, OPT may ask  
193 for additional information, which may include, for example, information regarding the past use  
194 of the investigational article in children or adults, documents regarding continuing review, the  
195 IND/IDE status, drug preparation protocol, or the certificate of analysis for the chemical being  
196 studied. During this exchange OPT will explain the procedures the agency intends to follow and  
197 will encourage the IRB to ask any questions it might have about the requirements of 21 CFR  
198 50.54.  
199

200 Following this exchange, the IRB may decide that it wishes to withdraw the referral from  
201 consideration. The reasons for withdrawal could include, for example, a misunderstanding of the  
202 requirements of the Subpart D regulations and the applicability of 50.54 to the clinical  
203 investigation at issue, i.e., a determination by the IRB after further analysis that the clinical  
204 investigation can in fact proceed under another provision in the Subpart D regulations.  
205 Withdrawal of a referral under circumstances such as these would be understandable and would  
206 avoid the unnecessary expenditure of agency and IRB resources. FDA suggests that an IRB in  
207 doubt about whether to refer a clinical investigation under 50.54 consult with OPT as soon as  
208 possible via email at [opt@fda.gov](mailto:opt@fda.gov).  
209

### **F. Assessment of Referral**

210  
211  
212 Following receipt of the referral, FDA will determine whether the protocol is FDA-regulated  
213 (generally within 2 weeks after receipt) and inform the referring IRB in writing of the  
214 determination. If the clinical investigation was referred to FDA by OHRP, FDA will also inform  
215 OHRP of that determination.  
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217 The considerations under FDA’s IND regulations (see 21 CFR Part 312) and IDE regulations  
218 (see 21 CFR Part 812) that are used to determine whether an IND or IDE can go into effect are  
219 related to, but distinct from, the considerations under Part 50 regarding the protection of human  
220 subjects. Therefore, IRBs should note that, although some clinical investigations are exempt  
221 from the need to be conducted under an IND (see 21 CFR 312.2(b)), those that are exempt are  
222 still subject to 21 CFR Parts 50 and 56 and thus may trigger the Subpart D process under section  
223 50.54. Similarly, a clinical investigation of a medical device may be exempt under 21 CFR  
224 812.2(c) from the requirement that it be conducted under an IDE, but the clinical investigation  
225 may still be subject to the Subpart D process. Furthermore, as indicated in 21 CFR 50.1(a), Part  
226 50 also applies to certain investigations that are not subject to sections 505(i) or 520(g) of the  
227 Federal Food, Drug, and Cosmetic Act (21 USC §§ 355(i), 360j(g)).  
228

### **G. Acceptance of Referral**

229  
230  
231 Following receipt of the referral, OPT will then ask the referring IRB for any other relevant  
232 documents and inform the IRB that FDA intends to post the documents in the docket created for  
233 the referral, and on the agency’s website. If the IRB believes that any documents it has included  
234 in its referral may be considered confidential by the sponsor, the IRB will be responsible for  
235 obtaining any necessary permission from the sponsor to post the documents. If an IRB (or  
236 sponsor) objects to the public posting of the documents, the agency will be unable to proceed  
237 with the referral.  
238

### **H. Multi-Site Clinical Investigations**

239  
240  
241 In some circumstances clinical investigations referred for review under 21 CFR 50.54 may be  
242 conducted at multiple sites. In the event that an IRB at one or more of the clinical sites refers the  
243 investigation for review, it should notify the sponsor. In such a situation, FDA strongly  
244 encourages the sponsor to notify the IRB(s) and principal investigator(s) at all of the other sites  
245 of the referral. Once an IRB has made a referral under 50.54, pursuant to that regulation the  
246 investigation may not proceed (i.e., no subjects should be recruited or enrolled in the  
247 investigation) at any site for which that IRB has responsibility.  
248

249 IRBs at other clinical sites may wish to allow the investigation to proceed despite being notified  
250 of the referral; IRBs at other sites should consider the implications of continuing the  
251 investigation during the pendency of the review and determination under 21 CFR 50.54. For  
252 example, at the conclusion of the review, it is possible that the Commissioner could determine  
253 that the investigation cannot proceed because one or more of the criteria in 21 CFR 50.54(b) are  
254 not met. Alternatively, the Commissioner might determine that the investigation can proceed but  
255 only with modifications of the protocol or the informed consent documents and procedures.  
256

### **I. Draft of Federal Register Notices**

257  
258  
259 Following a referral, FDA generally will issue three Federal Register notices:

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

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

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

266

### **J. Composition of the Pediatric Ethics Subcommittee**

267

268  
269 FDA will select the members of the Subcommittee in accordance with 21 CFR 50.54(b) and  
270 other relevant federal laws, including the Federal Advisory Committee Act (FACA) (5 U.S.C.  
271 App. 2)(1972). The Subcommittee will include at least two members of the PAC. FDA will also  
272 invite individuals to serve on the Subcommittee who have expertise and/or experience relevant to  
273 the clinical investigation being discussed. As a general matter, OPT will make these selections in  
274 collaboration with the relevant FDA Center(s) and review division(s). Additional individuals  
275 will be invited according to the principles set forth in 21 CFR 50.54(b), such that the  
276 Subcommittee consists of a “panel of experts in pertinent disciplines (for example: science,  
277 medicine, education, ethics, law)” (21 CFR 50.54(b)). As a general matter, FDA also believes  
278 that usually it will be helpful to include a patient advocate/community representative and a  
279 statistician on the Subcommittee.

280

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

284

### **K. The Subcommittee Meeting**

285

286  
287 FDA anticipates that a Subcommittee meeting usually will last for one day and a typical agenda  
288 will include:

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

302

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

305

### **L. PAC Meeting**

306  
307

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

317

### **M. Transmittal Memorandum**

318

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

327

### **N. Referral Process Timing**

328

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

331

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

332

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

336

- 337 • HHS, through OHRP, will participate in the selection of members for the Subcommittee.
- 338 • After the Subcommittee makes a recommendation to the PAC, the PAC will make its  
339 recommendation(s) to both the Secretary of HHS and the Commissioner of Food and  
340 Drugs.
- 341 • OPT will forward the Commissioner's determination to OHRP.
- 342 • OHRP will send a transmittal memo with its recommendation, the Commissioner's  
343 determination, and all supporting documents, including the recommendation(s) of the  
344 PAC and the summary of the Subcommittee meeting, to the Secretary for a determination  
345 as to whether the clinical investigation may be conducted or supported by HHS.
- 346
- 347