
Research Involving Children as Subjects and Not Otherwise Approvable by an IRB: Process for Referrals to FDA and OHRP Guidance for Institutional Review Boards, Institutions, Investigators, and Sponsors

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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For questions regarding this draft document, contact FDA (Office of Pediatric Therapeutics, Donna Snyder) at 301-796-1397, or the Office for Human Research Protections, Natalie Klein, at 240-453-6900 or 866-447-4777.

**U.S. Department of Health and Human Services
Food and Drug Administration (FDA)
Office of Pediatric Therapeutics (OPT)**

**U.S. Department of Health and Human Services
Office for Human Research Protections (OHRP)**

**March 2023
Procedural**

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Additional copies are available from:

Office of Pediatric Therapeutics

Office of Clinical Policy and Programs, Office of the Commissioner

Food and Drug Administration

10903 New Hampshire Avenue

Silver Spring, MD 20993

(Tel) 301-796-1397

and/or

Division of Policy and Assurances

Office for Human Research Protections

1101 Wootton Parkway, Suite 200

Rockville, MD 20852

Phone: 240-453-6900 688-447-4777

<http://www.hhs.gov/ohrp/newsroom/rfc/index.html>

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26 **Research Involving Children as Subjects and Not Otherwise**
27 **Approvable by an IRB:**
28 **Process for Referrals to FDA and OHRP**
29 **Guidance for Institutional Review Boards, Institutions, Investigators, and Sponsors**
30

31
32 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
33 Administration (FDA) and the Office for Human Research Protections (OHRP) on this topic. It does not
34 establish any rights for any person and is not binding on FDA, OHRP, or the public. You can use an
35 alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss
36 an alternative approach, contact the FDA or OHRP staff responsible for this guidance as listed on the title
37 page.
38

39
40 **I. INTRODUCTION**
41

42 This guidance is intended to assist institutional review boards (IRBs), institutions, investigators,
43 and sponsors in understanding the processes used for review of research involving children as
44 subjects that is not otherwise approvable by an IRB and has been referred to the Food and Drug
45 Administration (FDA) under 21 CFR 50.54, the Office for Human Research Protections (OHRP)
46 under 45 CFR 46.407, or both, for review.
47

48 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
49 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
50 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
51 the word should in Agency guidances means that something is suggested or recommended, but
52 not required.
53

54 **II. BACKGROUND**
55

56 The Department of Health and Human Services (HHS) issued 45 CFR part 46, subpart D,
57 “Additional Protections for Children Involved as Subjects in Research,” as a final rule on
58 March 8, 1983 (48 FR 9814). FDA issued 21 CFR part 50, subpart D, “Additional
59 Safeguards for Children in Clinical Investigations of Food and Drug Administration-
60 Regulated Products,” as a final rule on February 26, 2013 (78 FR 12937). These regulations,
61 hereinafter referred to collectively as “subpart D,” are similar, with some minor differences.¹
62

63 FDA’s subpart D regulations apply to clinical investigations² regulated by FDA as described

¹ For a full discussion of the differences between the FDA and HHS human subject protection regulations, see 78 FR 12937-12947.

² FDA’s regulations at 21 CFR 50.3(c) define *clinical investigation* as “any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted

64 in 21 CFR 50.1(a). HHS’s subpart D regulations apply to all research³ involving human
65 subjects and conducted or supported by HHS, in accordance with 45 CFR 46.101(a). FDA-
66 regulated clinical investigations conducted or supported by HHS are subject to both sets of
67 regulations. As a result, many sponsors,⁴ investigators,⁵ and IRBs need to be familiar with
68 and comply with both FDA’s and HHS’s regulations.⁶ Under both of these regulations, an
69 IRB must review research⁷ involving children as subjects under subpart D and may only
70 approve research satisfying the following applicable regulations (as well as the requirements
71 of all other applicable provisions of subpart D):
72

- 73 • 21 CFR 50.51 and 45 CFR 46.404: Research not involving greater than minimal risk.
- 74 • 21 CFR 50.52 and 45 CFR 46.405: Research involving greater than minimal risk but
75 presenting the prospect of direct benefit to the individual subjects.
- 76 • 21 CFR 50.53 and 45 CFR 46.406: Research involving no more than a minor increase
77 over minimal risk and no prospect of direct benefit to individual subjects, but likely to
78 yield generalizable knowledge about the subjects’ disorder or condition.
79

80 If an IRB does not find that research involving children as subjects meets the requirements of
81 21 CFR 50.51, 50.52 or 50.53 (FDA regulations); 45 CFR 46.404, 46.405 or 46.406 (HHS
82 regulations); or both as applicable, the research may proceed only if the following criteria in
83 21 CFR 50.54, 45 CFR 46.407, or both as applicable, are satisfied:
84

- 85 • The IRB finds that the research presents a reasonable opportunity to further the
86 understanding, prevention, or alleviation of a serious problem affecting the health or
87 welfare of children; and

later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.”

³ HHS regulations at 45 CFR 46.102(l) of the 2018 Requirements and 45 CFR 46.102(d) of the pre-2018 Requirements define *research* as “a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.” The 2018 Requirements at 45 CFR 102(l)(1)-(4) deem certain activities not to be research.

⁴ FDA’s regulations at 21 CFR 50.3(e) define *sponsor* as “a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

⁵ FDA’s regulations at 21 CFR 50.3(d) define *investigator* as “an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.”

⁶ The HHS regulations do not define the term *investigator*, however OHRP interprets an “investigator” to be any individual who is involved in conducting human subjects research studies. See

<https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/investigator-responsibilities/index.html>.

Due to the scope of the HHS regulations, this guidance refers to the *HHS division supporting or conducting the research* instead of *sponsor* when discussing HHS-conducted or -supported research.

⁷ Although the definitions of “clinical investigation” in FDA’s regulations and “research” in HHS’s regulations are different, for purposes of this guidance they are used interchangeably.

- 88 • The Commissioner of Food and Drugs (Commissioner), the Secretary of the Department
89 of Health and Human Services (HHS) (Secretary),⁸ or both as applicable, after
90 consultation with a panel of experts in pertinent disciplines (e.g., science, medicine,
91 education, ethics, law) and following opportunity for public review and comment,
92 determines either:
- 93 – The research in fact satisfies 21 CFR 50.51, 50.52 or 50.53; 45 CFR 46.404, 46.405,
94 or 46.406; or both sets of regulations as applicable, or
 - 95 – The following three conditions are met:
 - 96 1. The research presents a reasonable opportunity to further the understanding,
97 prevention, or alleviation of a serious problem affecting the health or welfare of
98 children;
 - 99 2. The research will be conducted in accordance with sound ethical principles;
100 and
 - 101 3. Adequate provisions are made for soliciting the assent of children and
102 the permission of their parents or guardians as set forth in 21 CFR
103 50.55, 45 CFR 46.408, or both as applicable.

104
105 An IRB may refer research involving children as subjects to FDA and/or OHRP for review
106 under 21 CFR 50.54 or 45 CFR 46.407, as applicable. Regardless of the agency to which the
107 referral is submitted, both FDA and OHRP intend to consult with each other on any referrals
108 received under 21 CFR 50.54 and 45 CFR 46.407 to ensure the appropriate agency has been
109 notified and to determine whether a joint review (i.e., a review by both FDA and OHRP) is
110 needed.

111
112 Consistent with 21 CFR 50.1(a), the requirements of 21 CFR part 50, subpart D, apply to
113 clinical investigations regulated under sections 505(i) and 520(g) of the Federal Food, Drug,
114 and Cosmetic Act (FD&C Act) (21 U.S.C. § 355(i) and 360j(g)), as well as those that support
115 applications for research or marketing permits for certain products regulated by FDA. The 21
116 CFR part 50, subpart D requirements are separate from the investigational new drug
117 application (IND) requirements in section 505(i) of the FD&C Act and 21 CFR part 312.
118 Therefore, 21 CFR part 50, subpart D, applies to all FDA-regulated clinical investigations of
119 drug or biological products, including those that are IND-exempt per 21 CFR 312.2(b)(iv).
120 Similarly, 21 CFR part 50, subpart D, applies to all FDA-regulated clinical investigations of
121 devices, including those that are exempt from most provisions of the investigational device
122 exemption (IDE) regulations under 21 CFR 812.2(c). Furthermore, as indicated in 21 CFR
123 50.1(a), part 50 also applies to certain clinical investigations of other types of FDA-regulated
124 products (e.g., food additives, infant formulas, new dietary ingredients). These clinical
125 investigations are also subject to the review process under 21 CFR 50.54.

126 127 **III. REFERRAL, REVIEW, AND OUTCOMES**

128
129 After making the required determinations (as described above), the IRB should refer the study
130 to FDA and/or OHRP following the details described below.

⁸ The Secretary's authority under Title IV of the Public Health Service Act (42 U.S.C. 281, et seq.) has been delegated to the Assistant Secretary for Health (ASH), 44 FR 46318 (August 7, 1979); see 67 FR 10216 (March 6, 2002).

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A. Referral

The following table outlines the process that should be followed when referring a study to FDA and/or OHRP for review. Where necessary, the differences between FDA and OHRP are identified.

FDA	OHRP
Address for referral: opt@fda.hhs.gov or Office of Pediatric Therapeutics (OPT) Office of the Commissioner Food and Drug Administration 10903 New Hampshire Avenue Silver Spring, MD, 20993	Address for referral: OHRP@hhs.gov or Division of Policy and Assurances Office for Human Research Protections Department of Health and Human Services 1101 Wootton Parkway, Suite 200 Rockville, MD 20852
A referral should include: <ul style="list-style-type: none"> • The IRB’s explanation of why the clinical investigation or proposed research does not meet the requirements of 21 CFR 50.51, 50.52, or 50.53 for FDA referrals; 45 CFR 46.404, 46.405, or 46.406 for OHRP referrals; • The IRB’s finding that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; • The research protocol, investigator’s name, current informed consent documents, including the parental/guardian permission form and, if being used, the assent form(s) and/or a description of the assent process; • Other informative supporting documents, such as the IRB minutes pertinent to the clinical investigation or proposed research, correspondence between the IRB and the investigator, investigational product labeling, the investigator’s brochure (IB), and the IRB’s assessment of investigator qualifications and research site adequacy; • IRB names and contact information (also include institution name for OHRP referrals) • For FDA referrals only: Investigational New Drug application (IND) or Investigational Device Exemption (IDE) numbers assigned by FDA if applicable and known • For OHRP referrals only: HHS application number (if applicable) and name of the HHS division conducting or supporting the research. Note: For HHS-supported research, OHRP will notify the relevant HHS division supporting the research of the request for review of the research under 45 CFR 46.407. 	

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FDA encourages IRBs to submit referrals to FDA as soon as an IRB determines that the clinical investigation can only proceed under 21 CFR 50.54. FDA also strongly encourages IRBs to submit all documents electronically and to submit optical character recognition (OCR)-enabled electronic versions of all documents. For instructions on submitting documents electronically to FDA, IRBs can contact OPT at opt@fda.hhs.gov or by phone at 301-796-1397. If an IRB is uncertain about whether to submit a clinical investigation for FDA review under 21 CFR 50.54, FDA recommends the IRB promptly consult FDA via email (opt@fda.hhs.gov). FDA will discuss with the IRB whether the clinical investigation meets the requirements for review under

148 21 CFR 50.54. FDA may request additional information from the IRB and/or contact the
149 relevant FDA office or review division to help determine whether the requirements for review
150 under 21 CFR 50.54 are met.

151
152 Similarly, OHRP encourages institutions or IRBs to submit referrals to OHRP as soon as an IRB
153 determines that the proposed research can only proceed under 45 CFR 46.407. OHRP also
154 strongly encourages referring institutions or IRBs to submit all documents electronically and to
155 submit OCR enabled electronic versions of all documents. For instructions on submitting
156 documents electronically, institutions or IRBs can contact OHRP at OHRP@hhs.gov or by
157 phone at (240) 453-6900. If an institution or IRB is uncertain about whether to submit a research
158 study for OHRP review under 45 CFR 46.407, OHRP recommends the institution or IRB
159 promptly consult OHRP via email (OHRP@hhs.gov). OHRP will discuss with the institution or
160 IRB whether the research meets the requirements for review under 45 CFR 46.407. OHRP may
161 request additional information from the institution or IRB and/or contact the relevant HHS
162 division supporting or conducting the research to help determine whether the requirements for
163 review under 45 CFR 46.407 are met.

164 165 **B. Assessment of Jurisdiction**

166
167 When FDA or OHRP receives a referral, either agency will contact the other in order to jointly
168 determine whether the study is FDA-regulated and/or HHS-supported or -conducted. If the
169 study is determined to be both FDA-regulated and HHS-supported or -conducted, FDA and
170 OHRP will coordinate their assessment of the referral as needed. In such cases, FDA and
171 OHRP generally intend to conduct a joint review of the research and will follow the process for
172 FDA-only assessment of referrals (See VII. PROCESS DIFFERENCES SPECIFIC TO JOINT
173 FDA AND OHRP REVIEW).

174 175 **C. Referral review and acceptance**

176
177 Depending on to whom the referral was submitted, FDA or OHRP will conduct an initial
178 assessment to determine whether there is adequate information to proceed with the referral. If the
179 information submitted is insufficient to enable FDA or OHRP to conduct this initial assessment,
180 the IRB (or institution) will be promptly notified of any needed information.

181
182 If the proposed research fulfills the criteria for consideration under the provisions of 21 CFR
183 50.54 (FDA) or 45 CFR 46.407 (OHRP), the referral will be accepted and the review process
184 will be initiated.

185
186 For reviews conducted by FDA, FDA will notify the appropriate FDA office and/or review
187 division to inform it that FDA has accepted a referral to review the clinical investigation under
188 21 CFR 50.54. FDA will provide written confirmation⁹ to the referring IRB that FDA has
189 accepted its referral. The IRB should inform the sponsor that a referral under 21 CFR 50.54
190 has been accepted by FDA.

191
192 For reviews conducted by OHRP, OHRP will notify the appropriate HHS division supporting

⁹ FDA may communicate with the IRB via electronic mail.

193 or conducting the research of the referral acceptance under 45 CFR 46.407. OHRP will provide
194 written confirmation of acceptance to the referring IRB and/or referring institution through mail
195 or email.

196
197 **D. Referral withdrawal**

198
199 If an IRB withdraws a referral from FDA or OHRP,¹⁰ the agencies encourage the IRB (or
200 institution) to include the reasons for withdrawal in its withdrawal request and in the IRB
201 meeting minutes.

202
203 **IV. Preparation for Pediatric Advisory Committee (PAC) and Pediatric Ethics**
204 **Subcommittee (PES) Meeting (FDA) or Expert Panel Meeting (OHRP)**

205
206 **A. Federal Register Notice and Docket**

207
208 FDA or OHRP will issue a Federal Register Notice (FRN) that will include the date and location
209 of the public meeting, the time available during the meeting for oral presentations from the public,
210 the establishment of a docket soliciting public comment on the referral, and instructions on how
211 to access the docket.¹¹

- 212
- 213 • After a referral is accepted by FDA, the Office of Pediatric Therapeutics (OPT) and the
214 relevant FDA office or review division, will prepare for presentation of the clinical
215 investigation to a joint meeting of FDA’s Pediatric Advisory Committee (PAC) and the
216 Pediatric Ethics Subcommittee (PES) (referred to in this guidance as the PAC/PES
217 meeting). FDA will identify for the referring IRB and/or sponsor, as appropriate, the
218 relevant documents (briefing materials) that the agency intends to post for the PAC/PES
219 meeting and that may be discussed during the PAC/PES meeting.¹² FDA will post the
220 briefing materials for the PAC/PES meeting on the FDA website. FDA intends to close
221 the docket 24 hours after the PAC/PES meeting because consideration of public comments
222 by the PAC/PES will have been completed.
 - 223 • Review of referrals to OHRP will be conducted by an expert panel comprised of
224 individuals selected for their expertise relevant to the specific referral. OHRP will post
225 referral materials in a public docket, including a notice that the panelists’ individual
226 recommendations will be publicly posted in the established docket after the expert panel
227 meeting. OHRP will identify for the referring IRB or referring institution and HHS
228 division supporting or conducting the research, as appropriate, the relevant documents

¹⁰ The IRB’s reasons for withdrawal of the referral could include, but are not limited to, a misunderstanding of the requirements of the subpart D regulations, a misinterpretation of the applicability of 21 CFR 50.54 or 45 CFR 46.407 to the clinical investigation, or submission of a protocol modification by the sponsor to the IRB such that the IRB determines the clinical investigation is approvable under another subpart D provision (i.e., 21 CFR 50.51, 50.52 or 50.53 or 45 CFR 46.404, 46.405 or 46.406).

¹¹ OHRP and FDA will post information about how to access the docket on their respective websites.

¹² For further information on the preparation of advisory committee briefing materials for FDA advisory committee meetings and the timelines for preparing and posting such materials, see FDA’s Guidance for Industry, Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members, available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/preparation-and-public-availability-information-given-advisory-committee-members>.

229 that it intends to post in the public docket. To allow time for public comments on the
230 panelists' individual recommendations, the docket will remain open for 30 days after the
231 date of the expert panel meeting.
232

233 **B. Documents and Public Review**
234

235 The documents supporting the referral¹³ may include information that, under certain
236 circumstances, could be considered confidential and exempt from public disclosure. This
237 information may include trade secret information (TSI), confidential commercial information
238 (CCI), or personal privacy information (PPI) (including personally identifiable information).
239

240 After obtaining any necessary agreements and permissions from the IRB and/or sponsor, as
241 discussed below, and documents are appropriately redacted, the agency will publicly post the
242 referral documents (on FDA's website, for referrals to FDA, and in a public docket, for
243 referrals to OHRP) as soon as possible after the public announcement of the meeting in the
244 Federal Register.
245

246 *FDA-specific information:*

247 All FDA advisory committee members who are special government employees have access to
248 nonpublic information in advisory committee briefing materials and are bound by the same
249 confidentiality protections as all other government employees. The PAC/PES members will be
250 reminded that TSI, CCI, and PPI must not be revealed during the PAC/PES meeting.
251

252 As noted above, FDA will identify for the referring IRB and/or sponsor, as appropriate, the
253 relevant documents that the agency intends to post for the PAC/PES meeting to meet the
254 requirement for public review and comment and that may be discussed during the PAC/PES
255 meeting. As appropriate, the agency will include redactions of information that could be
256 considered TSI, CCI, or PPI. If the IRB and/or sponsor objects to the disclosure of any
257 documents or information identified by FDA for public posting and discussion, FDA will work
258 with the IRB and/or sponsor to ensure that any redactions will not negatively impact either the
259 opportunity for public review and comment that is required under the regulation or the
260 discussion of the clinical investigation at the PAC/PES meeting.
261

262 If redactions requested by the IRB and/or sponsor are such that either the requirement for an
263 opportunity for public review would not be met or the discussion at the PAC/PES meeting
264 would be significantly limited, FDA may be unable to proceed with the referral. If this were to
265 occur, the clinical investigation would not be authorized to proceed. If the IRB and/or sponsor,
266 as appropriate, agrees to the public availability of the documents or information identified by
267 FDA (either with or without redactions), FDA will work with the IRB and/or sponsor to
268 document the agreement.
269

270 FDA will schedule the PAC/PES meeting based on the urgency of the request.¹⁴ FDA will

¹³ Documents supporting the referral include, e.g., the research protocol, parental/guardian permission and assent forms, and IRB meeting minutes.

¹⁴ The PAC is currently scheduled to meet approximately two times per year. The PES is convened on an as-

271 schedule the PAC/PES meeting directly preceding a regularly scheduled PAC meeting or will
272 expedite consideration of the referral by convening a separate PAC/PES meeting scheduled
273 specifically to handle the referral.¹⁵

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275

276 *OHRP specific information:*

277 All expert panel members will be bound by confidentiality agreements and informed that TSI,
278 CCI, and PPI will not be discussed during the panel’s public deliberations.

279

280 As noted above, OHRP will identify for the referring IRB or referring institution and HHS
281 division supporting or conducting the research, as appropriate, the relevant documents that it
282 intends to post in the public docket. OHRP reserves the right to permit redactions prior to
283 including the documents supporting the referral in the public docket. OHRP will work with the
284 IRB or referring institution or HHS division supporting or conducting the research to ensure
285 that the information redacted will not impact public review and discussion of the research. If
286 the IRB or referring institution or HHS division supporting or conducting the research objects
287 to the disclosure of any nonpublic documents or information in the documents identified by
288 OHRP for public posting and discussion, OHRP will work with the IRB or referring institution
289 and/or sponsor to ensure that any redactions will not negatively impact either the opportunity
290 for public review and comment that is required under the regulation or the discussion of the
291 research at the expert panel meeting.

292

293 If redactions requested by the IRB or referring institution and/or HHS division supporting or
294 conducting the research are such that either the requirement would not be met or the discussion
295 at the expert panel meeting would be significantly limited, OHRP may be unable to proceed
296 with the referral. In this case, the research protocol would not be authorized to proceed. If the
297 IRB or HHS division supporting or conducting the research, as appropriate, agrees to the public
298 availability of the documents or information (either with or without redactions) identified by
299 OHRP, OHRP will work with the IRB or HHS division to document the agreement.

300

301 **V. PAC/PES (FDA) or Expert Panel (OHRP) Meeting**

302

303 **A. Composition**

304

305 FDA selects the members of the PAC/PES in accordance with 21 CFR 50.54(b) and other
306 relevant federal laws and regulations, including the Federal Advisory Committee Act (FACA)
307 (5 U.S.C. App. 2) (1972). FDA will invite additional individuals to participate on the PAC/PES
308 to ensure the subcommittee consists of a “panel of experts in pertinent disciplines (for example:
309 science, medicine, education, ethics, law).”¹⁶

needed basis to address ethics issues as they arise. For the purposes of a 21 CFR 50.54 review, the meeting will always be held as a joint PAC/PES meeting.

¹⁵ A minimum of 8 to 10 weeks is generally necessary between the acceptance of the referral and the PAC/PES meeting date because of the time needed to issue the FRN announcing the meeting and prepare the relevant materials (see Sections III.E.4 and III.E.5). Thus, unless a referral is submitted more than 8-10 weeks in advance of an already scheduled PAC meeting, it generally will not be possible to add the referral to the agenda for that meeting.

¹⁶ See 21 CFR 50.54(b).

310
311 OHRP will identify a panel of experts in pertinent disciplines per 45 CFR 46.407(b) (e.g.,
312 science, medicine, education, ethics, law), and child advocates with experience relevant to the
313 protocol, to review the research. Potential experts will be informed that they will each provide
314 written recommendations discussing whether the proposed research satisfies the criteria at
315 46.407(b)(1) or (2), and that their recommendations, as well as their identity as the author of the
316 recommendations, will be publicly available in the docket for public review and comment.

317
318 **B. Attendees**

319
320 The meeting will be open to the public and public participation is encouraged. The agencies
321 encourage the IRB, the sponsor (if appropriate), and the investigator(s) to attend the meeting to
322 assist the members in understanding the clinical investigation or proposed research and provide
323 an opportunity for the members to ask questions regarding the basis for the referral.

324
325 As appropriate, additional individuals (e.g., representative(s) from patient advocacy group(s),
326 subject matter expert(s)) will be invited to make presentations regarding the referred clinical
327 investigation/proposed research or related issues of concern.

328
329 For PAC/PES meetings, FDA will invite the referring IRB and the sponsor to present relevant
330 information about the clinical investigation at the meeting. One or more representatives from the
331 FDA office and/or review division responsible for reviewing the clinical investigation also may
332 attend the PAC/PES meeting to answer questions about the clinical investigation or any related
333 issues.

334
335 **C. Meeting Content**

336
337 Although an IRB (or institution) may make a referral for review because of a particular aspect
338 of the clinical investigation or proposed research (e.g., entry criteria, planned procedure), the
339 agencies intend to request input and recommendations on the clinical investigation or proposed
340 research in its entirety.

341
342 The chair of the meeting will provide a summary of public comments submitted to the docket
343 before the meeting.

344
345 **D. Recommendation(s)**

346
347 For PAC/PES meetings, after deliberation and discussion of the clinical investigation, the
348 PAC/PES will vote on whether to recommend that the proposed clinical investigation may
349 proceed under 21 CFR 50.51, 50.52, 50.53 or 50.54.¹⁷ The PAC/PES members will not write
350 individual recommendations regarding whether the research meets the criteria in 21 CFR
351 50.54(b)(1) or (2).

352

¹⁷ Although the PAC/PES meeting will focus on whether the clinical investigation is approvable under 21 CFR part 50 subpart D, the clinical investigation also must comply with all other applicable requirements, including but not limited to those in 21 CFR part 50, subparts A and B, and in 21 CFR part 56.

353 For OHRP expert panel meetings, after deliberation and discussion of the proposed research,
354 each panel member will write an individual recommendation discussing whether the research
355 meets the criteria of 45 CFR 46.407(b)(1) or (2). OHRP will post the individual panel member
356 recommendations in the docket. To allow time for comments on the posted expert panel
357 recommendations, the public may continue to provide comments in the docket for 30 days after
358 the date of the expert panel meeting.

359
360

361 **VI. Final Determination**

362

363 *FDA specific information:*

364 After the PAC/PES meeting, FDA staff will develop and send a memorandum that outlines the
365 PAC/PES recommendation(s) and that includes any FDA staff comments and
366 recommendations, as well as relevant supporting documents, to the FDA Commissioner (or
367 delegee). The memorandum may include recommended changes to the research protocol and/or
368 changes to the parental/guardian permission and assent forms that the PAC/PES and/or FDA
369 staff believe are necessary for the clinical investigation to proceed under subpart D, as well as
370 any suggested changes that might enhance the clinical investigation (e.g., strategies to ease study
371 burden on patients and care providers, strategies to improve trial enrollment). The
372 memorandum will request the Commissioner (or delegee) make a final determination as to
373 whether, and if so, under which provisions of subpart D, the clinical investigation may
374 proceed.

375

376 After the Commissioner (or delegee) has made a final determination, FDA intends to forward
377 the determination to the IRB and post the final determination on the FDA website within 90
378 days of the PAC/PES meeting or as soon as practicable thereafter. FDA will post the
379 PAC/PES transcripts and meeting documents on the FDA website when available.

380

381 *OHRP specific information:*

382 After the OHRP expert panel meeting, OHRP will develop a recommendation for the Assistant
383 Secretary for Health (ASH) based on panel deliberations, reports, public comments, and its own
384 analysis. The recommendation may include changes to the research protocol and/or changes to
385 the parental/guardian permission and assent forms that an expert panelist or OHRP staff believe
386 are necessary for the research to proceed under subpart D, as well as any suggested changes that
387 might enhance the research (e.g., strategies to ease study burden on patients and care providers,
388 strategies to improve trial enrollment). OHRP then will submit its recommendation and relevant
389 documents to the ASH. After review of the relevant materials and OHRP's recommendation, the
390 ASH, on behalf of the HHS Secretary, will make the final determination regarding whether the
391 research may proceed under 45 CFR 46.404, 46.405, 46.406, or 46.407.

392

393 OHRP will inform the referring institution and/or IRB chair, the investigator, and the HHS
394 division supporting or conducting the research of the ASH's determination and post its
395 recommendation to the ASH and the ASH's final determination in the established docket within
396 90 days of the expert panel meeting or as soon as practicable thereafter.

397

398 **VII. PROCESS DIFFERENCES SPECIFIC TO JOINT FDA AND OHRP REVIEW**

399

400 As noted above, for research that FDA and OHRP determine is both HHS-conducted or -
401 supported and FDA-regulated, FDA and OHRP generally intend to conduct a joint review of the
402 research and will follow the process for FDA-only assessment of referrals. Unique aspects of
403 the joint subpart D review process include:

- 404 • FDA will communicate with the IRB and sponsor, and institution if appropriate, on
405 behalf of both FDA and OHRP.
- 406 • FDA will post documents related to the joint review to the FDA website. OHRP will not
407 post documents to a federal docket and will instead post a link to the FDA website on the
408 OHRP website.
- 409 • FDA will convene a PAC/PES meeting, which will serve as the expert panel meeting for
410 both FDA and OHRP (see Section IV).
 - 411 – OHRP will participate with FDA in the selection of members for the PAC/PES meeting;
 - 412 – OHRP will participate with FDA in the PAC/PES meeting.
- 413 • The ASH, acting on behalf of the Secretary, will make the determination whether the
414 research is approvable under 45 CFR 46.407 after the FDA Commissioner (or delegee)
415 has determined whether the clinical investigation is approvable under 21 CFR 50.54.
 - 416 – After the PAC/PES makes its recommendation(s) on whether the clinical
417 investigation may proceed under 21 CFR part 50, subpart D, and 45 CFR part 46,
418 subpart D, FDA staff will submit a memorandum outlining the PAC/PES
419 recommendation(s), FDA staff recommendations, and the supporting documents to
420 the FDA Commissioner (or delegee).
 - 421 – The FDA Commissioner (or delegee) will determine whether the clinical
422 investigation may proceed under 21 CFR 50.54.
 - 423 – FDA will forward a memorandum outlining the PAC/PES recommendation(s), FDA
424 staff recommendations, and the Commissioner’s (or delegee’s) determination to
425 OHRP.
 - 426 – OHRP will formulate a recommendation to the ASH based on the findings of the
427 PAC, the FDA Commissioner’s (or delegee’s) determination, public comments, and
428 OHRP internal review.
 - 429 – OHRP will send a memorandum with the PAC/PES recommendation(s), the FDA
430 Commissioner’s (or delegee’s) determination, OHRP’s recommendation(s) and all
431 supporting documents to the ASH. The ASH, acting on behalf of the Secretary, will
432 make the determination whether the research may proceed under 45 CFR 46.404,
433 46.405, 46.406, or 46.407.

434
435 Determinations of the ASH and the FDA Commissioner (or delegee) will be posted by FDA
436 and OHRP and forwarded to the referring IRB or referring institution, investigator, and/or HHS
437 Division, as appropriate, within 90 days of the PAC/PES meeting or as soon as practicable
438 thereafter.

439
440 **VIII. MULTISITE RESEARCH**
441

442 In some circumstances, research referred for review under FDA and/or HHS regulations might

443 be conducted at multiple sites or institutions, and as such, be reviewed by more than one IRB.¹⁸
444 If an IRB for one or more of the clinical sites refers the research for review, the IRB should
445 notify the sponsor or HHS division supporting or conducting the research. In this situation,
446 FDA and OHRP strongly encourage the sponsor or relevant HHS division to notify all other
447 study site IRB(s) and investigator(s) of the referral.
448

449 For multisite research regulated by FDA and conducted under an IND or IDE, if an IRB makes
450 a referral under 21 CFR 50.54, FDA will determine whether the clinical investigation may
451 proceed (or continue, if enrollment has already begun at one or more sites) or will be placed on
452 clinical hold.¹⁹ In the case of a referral regarding an investigation for which an IDE application
453 (or supplement) is pending, FDA may also consider other actions.²⁰ If FDA concludes that a
454 clinical hold is appropriate, the agency generally intends to apply that clinical hold to all sites,
455 regardless of whether IRBs other than the one that referred the protocol have approved the
456 protocol. While the 21 CFR 50.54 review is underway, FDA will inform the sponsor whether
457 the clinical investigation has been placed on clinical hold and the sponsor must then notify
458 investigators if the clinical investigation has been placed on clinical hold.²¹ The sponsor also
459 should inform the other study site IRBs.²²
460

461 For multisite research regulated by OHRP, that does not require, or is excepted from the
462 requirement for, single IRB review under 45 CFR 46.114, the HHS division supporting or
463 conducting the research may consider the implications of the 45 CFR 46.407 review process on
464 the conduct of the research at other HHS supported sites and whether, if consistent with
465 applicable law, to delay or suspend subject enrollment at these other sites pending the outcome
466 of the 45 CFR 46.407 review.
467

468 **IX. FDA AND OHRP REVIEW OF SIMILAR RESEARCH**

469
470
471 FDA and OHRP recognize that there may be situations in which it would be appropriate for the
472 Commissioner (or delegee) and/or the ASH to rely on previous PAC/PES or expert panel
473 consideration of a similar research protocol in order to review a newly referred protocol. FDA
474 and OHRP note that the subpart D regulations do not specify that the expert panel review of the
475 research must occur after the IRB referral for review.
476

477 FDA and/or OHRP will consider reviewing research submitted to FDA and/or OHRP for subpart
478 D review under an abbreviated process if the research is similar to research that FDA and/or
479 OHRP has already reviewed under subpart D and determined may proceed. This abbreviated

¹⁸ Under 45 CFR 46.114, any institution located in the United States that is engaged in cooperative research (i.e., research that involves more than one institution) must rely upon approval by a single IRB for that portion of the research that is conducted in the United States (45 CFR 46.114(b)(1)) unless one of the exceptions at 45 CFR 46.114(b)(2) applies.

¹⁹ For clinical investigations being conducted under an IND, see 21 CFR 312.42(b). For clinical investigations being conducted under an IDE, see section 520(g)(8) of the FD&C Act.

²⁰ FDA may approve, approve with conditions, or disapprove a pending IDE application. See 21 CFR 812.30.

²¹ 21 CFR 312.42(a), 312.50, and 812.40.

²² For device investigations that require submission of an IDE application, sponsors must ensure that any reviewing IRB is promptly informed of significant new information about an investigation. 21 CFR 812.40.

480 process would necessitate that FDA and/or OHRP determine the newly referred research is
481 sufficiently similar to the previously reviewed research such that the previous referral and review
482 are applicable to the newly referred research; such determinations are anticipated to be rare.

483
484 If FDA and/or OHRP conduct an abbreviated review process, FDA and/or OHRP will include in
485 the information posted to the FDA website and/or OHRP docket (see Section III.E.2 and IV.E.2)
486 the determination by the Commissioner and/or ASH for the previous referral as well as relevant
487 background information from the previous referral. FDA and/or OHRP will publish an FRN to
488 solicit public comments on the newly referred research. For FDA subpart D reviews conducted
489 under an abbreviated process, the FRN will include a link to the relevant documents and
490 background information on the FDA website, notice of the establishment of a docket for
491 comments, and directions for accessing the docket. For OHRP subpart D reviews conducted
492 under an abbreviated process, the FRN will include notice of the establishment of a docket for
493 posting relevant documents and background information and comments, and directions for
494 accessing the docket. The docket will remain open for 30 days.

495
496 The responsible agency(ies) will review the public comments submitted to the newly established
497 docket(s). Based on the review of comments, FDA and/or OHRP may either decide a
498 determination may be issued without additional PAC/PES or expert panel review, or that a new
499 PAC/PES or expert panel review is needed. If a new PAC/PES meeting or expert panel is
500 convened, the review under the subpart D regulations will proceed as outlined above.
501 Alternatively, FDA and/or OHRP may decide that no further PAC/PES or expert panel review
502 are necessary. In this situation, FDA and/or OHRP will prepare a recommendation for the
503 Commissioner (or delegee) and/or ASH and the subsequent final determination by the
504 Commissioner (or delegee) and/or ASH regarding the newly referred protocol will be posted to
505 the FDA website, with a reference to the FDA docket, and/or will be posted to the OHRP docket,
506 as applicable.