
Guidance for IRBs, Clinical Investigators and Sponsors

IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)**

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14 **Guidance for IRBs, Clinical Investigators, and Sponsors¹**
15 **IRB Responsibilities for Reviewing the Qualifications of**
16 **Investigators, Adequacy of Research Sites, and the Determination of**
17 **Whether an IND/IDE is Needed**
18

19
20 This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current
21 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
22 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
23 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
24 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
25 the appropriate number listed on the title page of this guidance.
26

27
28
29
30 **I. INTRODUCTION**
31

32 FDA is issuing this guidance to remind institutional review boards (IRBs) of their longstanding
33 role in the review of 1) the qualifications of the clinical investigator, 2) the adequacy of the
34 facility in which the research will take place, and 3) the determination of whether an
35 investigational new drug application (IND) or investigational device exemption (IDE)
36 application is necessary for the proposed clinical investigation.
37

38 FDA’s guidance documents, including this guidance, do not establish legally enforceable
39 responsibilities. Instead, guidances describe the agency’s current thinking on a topic and should
40 be viewed only as recommendations, unless specific regulatory or statutory requirements are
41 cited. The use of the word *should* in agency guidances means that something is suggested or
42 recommended, but not required.
43

44 To enhance human subject protection and reduce regulatory burden, the Department of Health
45 and Human Services (HHS) Office for Human Research Protections (OHRP) and FDA have
46 been actively working to harmonize the agencies’ regulatory requirements and guidance for
47 human subject research. This draft guidance document was developed as a part of these efforts
48 and in consultation with OHRP.
49

50 **II. BACKGROUND**
51

52 Many of the recommendations in this guidance have appeared in other FDA guidance
53 documents² or have been communicated to IRBs who have contacted the agency directly about

¹ This guidance has been prepared by FDA’s Institutional Review Board Working Group, which includes representatives from FDA’s Office of the Commissioner, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), and Office of Regulatory Affairs (ORA).

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54 these issues.³ FDA has also provided instructions to its field investigators on the types of
55 documentation that should be reviewed during an IRB inspection to determine whether the IRB
56 has established and followed its written procedures with respect to reviewing an investigator's
57 qualifications, the adequacy of a site, and the determination of whether an IND or IDE is
58 necessary.⁴ FDA has compiled the advice from these various sources into this guidance to
59 ensure that all IRBs have access to it. In addition, FDA provides guidance on how IRBs may
60 efficiently fulfill these important responsibilities.

61

III. DISCUSSION

62

1. Must an IRB review the qualifications of clinical investigators who conduct FDA-regulated research?

63

64 Yes. Although FDA's regulations place responsibility on the sponsor to select clinical
65 investigators who are "qualified by training and experience as appropriate experts" to investigate
66 the test article,⁵ IRBs also have a role in reviewing an investigator's qualifications.⁶ The
67 regulations at 21 CFR 56.107(a) require that an IRB be able to ascertain the acceptability of the
68 proposed research in terms of institutional commitments and regulations, applicable law, and
69 standards of professional conduct and practice. In addition, the regulations at 21 CFR 56.111
70 require that an IRB determine that the proposed research satisfies the criteria for approval,
71 including that the risks to subjects are minimized and reasonable in relation to anticipated
72 benefits, if any, to subjects. In order to fulfill these responsibilities, the IRB needs information
73 about the qualifications of the investigator(s) to conduct and supervise the proposed research.

74

75 Depending upon the nature and risks of the proposed research and the relationship between the
76 IRB and the investigator or the institution where the proposed research is being conducted, this
77 may be relatively simple and straightforward or it may entail a more involved assessment.

78

79 In many cases, the IRB may have previous experience with an investigator or institution that
80 would allow the IRB to readily determine that the clinical investigator is appropriately qualified
81 to conduct and supervise the proposed research. In other cases, the IRB may need additional
82 information; however, the IRB should be able to easily obtain a statement confirming the
83 investigator's qualifications from an administrator of the institution. For example, for proposed
84 research to be conducted at a hospital where only credentialed hospital staff may conduct
85 research, the IRB may be able to rely on another office at the institution (e.g., the credentialing

86

² ICH E6 *Good Clinical Practice: Consolidated Guidance, 3.1.3*,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf>;
and FDA Guidance, *Using a Centralized IRB Review Process in Multicenter Clinical Trials*, Section IV (in relevant
part, speaks to the "capacity of the institution to conduct or support the proposed research")

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127013.pdf>.

³ <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriesToFDAonGoodClinicalPractice/default.htm>.

⁴ Compliance Program Guidance Manual (CPGM) 7348.809, Institutional Review Boards, November 28, 2011,
generally, and Section III.J, K, and U.;

<http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133768.pdf>.

⁵ 21 CFR 312.53(a); see also 21 CFR 812.43(a).

⁶ See 21 CFR 56.102(g), (h), and (j) for definitions of IRB, investigator, and sponsor, respectively;

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm>.

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89 office, the clinical investigator's medical department) for an assessment of the clinical
90 investigator's qualifications. For proposed research to be conducted by a university faculty
91 member (e.g., at an affiliated hospital or clinic), the IRB may be able to obtain a statement
92 regarding the investigator's qualifications from the chair of the investigator's department.
93

94 On the other hand, if the reviewing IRB has no knowledge of either the clinical investigator or
95 the institution (e.g., the IRB is not affiliated with the institution where the research will be
96 conducted; the IRB has no previous experience with the investigator), the IRB would likely need
97 to take additional steps to evaluate the investigator's qualifications (e.g., reviewing the
98 curriculum vitae of the investigator, subinvestigators, and other necessary study staff; verifying
99 professional associations and medical licensure; reviewing relevant publications).

100
101 The IRB may also need to assess the investigator's training and experience specifically related to
102 the proposed study, particularly if the proposed research involves higher risks, vulnerable
103 subjects, or novel technologies or surgical techniques. For such proposed research, the IRB's
104 determination that the investigator is qualified may need to include a review of the investigator's
105 previous specific experience both in this field (e.g., as demonstrated by recent presentations or
106 publications), and prior experience with the test article. In addition, the IRB should pay
107 particular attention to investigator's qualifications to conduct a study submitted for approval to
108 the IRB if the study involves one or more of the following:

- 109 • a sponsor-investigator;⁷
- 110 • a study that is outside of the investigator's area of expertise; or
- 111 • any study design features or other characteristic(s) that may significantly increase
112 potential risks to subjects.
113

114
115 The IRB may also elect to observe, or have a third party observe, the consent process and the
116 research (21 CFR 56.109(f)), particularly if any concerns remain about the investigator's
117 qualifications or experience.
118

119 Appropriately trained IRB support staff may assist in obtaining and assessing information about
120 an investigator's qualifications. FDA recommends that the IRB's procedures describe the IRB's
121 process for evaluating the investigator's qualifications to conduct and supervise the study.
122

2. Is any information publicly available from FDA about a clinical investigator's inspectional history?

123
124
125
126 Yes. IRBs may check the lists posted on FDA's website to determine whether a clinical
127 investigator has been the subject of an inspection by the agency⁸ and the results of such

⁷ FDA's regulations (21 CFR 312.53(a) and 21 CFR 812.43(a)) require that a sponsor select clinical investigators who are "qualified by training and experience" to investigate the test article. In a sponsor-investigator (S-I) clinical trial, the S-I assumes the responsibilities of both the sponsor and the investigator (see 21 CFR 312.3(b) and 21 CFR 812.3(o)); therefore, there is no independent assessment of the clinical investigator's qualifications by the study sponsor. In this case, the IRB's review of the investigator's qualifications is particularly important to the determination that the risks to subjects are minimized and reasonable in relation to anticipated benefits, if any, to subjects.

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128 inspections (e.g., Warning Letters).⁹ FDA also posts on its website a listing of all investigators
129 who have been notified of the initiation of a disqualification proceeding¹⁰ and a listing of all
130 disqualified investigators.¹¹ FDA recommends that IRBs routinely check FDA's compliance and
131 enforcement websites for information related to clinical investigator inspections and
132 disqualification proceedings.

133

3. *Must an IRB review the adequacy of the research site?*

134

135
136 Yes. FDA's regulations require that before an IRB can approve research covered by the
137 regulations, the IRB must be able to ascertain the acceptability of the proposed research in terms
138 of institutional commitments and regulations, applicable law, and standards of professional
139 conduct and practice.¹² The regulations also require that each IRB have sufficient information to
140 determine that the proposed research satisfies the criteria for approval.¹³

141

142 In the great majority of instances, an IRB will likely be familiar with the research site or
143 institution at which the clinical investigator has proposed to conduct the research; in such cases,
144 additional assessment of a site's adequacy will probably not be necessary (for example, if the
145 research is to be conducted at the IRB's affiliated institution). In other cases, the IRB may need
146 additional information in order to assess the site where the proposed research will take place to
147 ensure it can adequately execute the protocol requirements. Depending upon the nature and risks
148 of the proposed research and the IRB's prior knowledge of or relationship to the institution or
149 other site at which the research will take place, this may be relatively simple and straightforward
150 or it may entail a more involved assessment.

151

152 For example, if a proposed clinical investigation involves administration of medical procedures
153 by qualified healthcare providers using medical equipment, the IRB should be prepared to assess
154 the adequacy of the facility's staff and equipment, including the availability of emergency or
155 specialized care if the need should arise. If the proposed research site is part of a major medical
156 institution, the IRB would likely be able to simply note that fact. If, however, the IRB is
157 unfamiliar with the proposed investigational site (e.g., research facility, hospital, physician's
158 office, dental clinic), the IRB would likely need to confirm whether the site is appropriately
159 staffed and equipped to conduct the proposed research. The IRB should be able to obtain a
160 statement from an appropriate person or persons at the research site or institution stating that the
161 facilities are adequate. Alternatively, the IRB could ask that the investigator provide a

⁸ Lists of investigators who have been inspected by FDA for CDER are posted at:
<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ComplianceEnforcement/default.htm>;
for CBER:

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/ucm165743.htm>. Investigators who conducted a device study from 2009 to present are included in the Inspection Classification Database maintained by FDA's Office of Regulatory Affairs at:
<http://www.accessdata.fda.gov/scripts/inspsearch>.

⁹ See the agency's Electronic Reading Room, including Warning Letters
(<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm>).

¹⁰ See <http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm092185.htm>.

¹¹ See <http://www.fda.gov/ICECI/EnforcementActions/DisqualifiedRestrictedAssuranceList/ucm131681.htm>.

¹² 21 CFR 56.107(a).

¹³ 21 CFR 56.111(a).

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162 description of the facility where the research will take place, including its staffing and resources
163 relevant to the research under review.

164
165 **4. What are the IRB's responsibilities with respect to verifying the determination of whether**
166 **an IND or IDE is required for an FDA-regulated investigation?**

167
168 The IRB's specific responsibilities vary, depending on the product that is the subject of the study;
169 however, in general, the IRB should ask the investigator whether he/she considered the need to
170 obtain an IND or IDE and the basis for any determination as to whether an IND/IDE is or is not
171 needed.

172
173 **Drug and Biologics Studies.** FDA regulations require sponsors and clinical investigators to
174 determine whether an IND is necessary for a particular study.¹⁴ The sponsor (or sponsor-
175 investigator of an individual investigator-initiated study) should be able to determine whether the
176 IND regulations apply to a planned clinical investigation as required under 21 CFR 312.2(a). If a
177 sponsor is uncertain, however, we recommend that the sponsor contact the appropriate review
178 division (i.e., for the therapeutic area being studied) in the appropriate FDA Center for advice
179 about whether the IND regulations apply (21 CFR 312.2(e)).

180
181 When reviewing a proposed study, IRBs should ask the clinical investigator whether an IND is
182 or is not required and the basis for the determination. If the sponsor or investigator has
183 determined that an IND is not needed, the IRB may request that the investigator provide a copy
184 of any available documentation about the need for an IND (e.g., letter from the sponsor or FDA,
185 other basis for that determination). If during its initial review of a study, the IRB questions
186 whether an IND is necessary, but is unable to resolve this issue, the IRB should follow its
187 procedures for resolving controverted issues (e.g., notifying the clinical investigator in writing of
188 the IRB's concerns¹⁵ and delaying approval of the study until the matter is resolved). FDA
189 issued for public comment the *Draft Guidance for Industry: Investigational New Drug*
190 *Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted*
191 *Without an IND.*¹⁶ When finalized, the guidance will represent FDA's current thinking on this
192 topic.

193
194 Organizational charts listing the review divisions for the Center for Drug Evaluation and
195 Research (CDER) and the Center for Biologics Evaluation and Research (CBER) and their
196 phone numbers are available on FDA's website.¹⁷ If the relevant review division is not known,
197 the sponsor may contact CDER or CBER directly:

198
199 CDER: Office of Communications, Division of Drug Information
200 Center for Drug Evaluation and Research
201 Food and Drug Administration

¹⁴ See 21 CFR 312.2, 312.20, 312.50, and 312.60. Studies that are exempt from the IND requirements are required, however, to comply with 21 CFR Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards).

¹⁵ 21 CFR 56.109(e)

¹⁶ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM229175.pdf>.

¹⁷ CDER: <http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135674.htm>;

CBER: <http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135943.htm>.

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206 CBER: Office of Communication, Outreach and Development¹⁸
207 Center for Biologics Evaluation and Research
208 Food and Drug Administration
209 1401 Rockville Pike, Suite 200N
210 Rockville, MD 20852-1448
211 (Tel) 800-835-4709 or 301-827-1800
212

213 **Device Studies.** The sponsor is responsible for determining whether submission of an IDE
214 application to FDA is required before a study may proceed.¹⁹ The IDE regulations (21 CFR 812)
215 describe three types of device studies: significant risk (SR), nonsignificant risk (NSR), and
216 exempt studies.²⁰ SR device studies must have an IDE application approved by FDA before they
217 proceed, and they must follow all of the IDE requirements.²¹ NSR device studies must follow
218 the abbreviated IDE requirements at 21 CFR 812.2(b) and do not require submission of an IDE
219 application to FDA.

220
221 The sponsor is responsible for making the initial risk determination, SR or NSR, and presenting
222 it to the IRB.²² If the sponsor has determined that a device study is NSR, the IRB must review
223 the sponsor's determination.²³ If the IRB disagrees with the sponsor's NSR assessment and
224 decides the study is SR, the IRB must inform the clinical investigator and, where appropriate, the
225 sponsor.²⁴
226

227 FDA is available to assist sponsors, investigators, and IRBs in making these determinations. For
228 information on how to request such assistance, please see the guidance *Procedures for Handling*
229 *Inquiries Regarding the Need for an Investigational Device Exemptions Application for*
230 *Research Involving Medical Devices.*²⁵ Sponsors, clinical investigators, and IRBs who need
231 assistance in making a risk determination for a medical device may also contact:
232

233 IDE Staff
234 Office of Device Evaluation
235 Center for Devices and Radiological Health
236 Food and Drug Administration
237 10903 New Hampshire Avenue
238 Silver Spring, MD 20993-0002

¹⁸ <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm106001.htm>.

¹⁹ 21 CFR 812.2(b)(1)(ii).

²⁰ With the exception of 21 CFR 812.119, exempt studies are not subject to the IDE regulations. 21 CFR 812.2(c). Exempt studies are required to comply with 21 CFR Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards).

²¹ 21 CFR 812.20(a)(1) and (2).

²² 21 CFR 812.2(b)(1)(ii).

²³ 21 CFR 812.2(b)(1)(ii).

²⁴ 21 CFR 812.66.

²⁵ <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm126598.htm>.

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239 (Tel) 301-796-5640

240

241 Based on the information provided, FDA will determine if a device study is SR, NSR, or exempt
242 from the IDE requirements found in 21 CFR Part 812. If FDA makes the SR or NSR
243 determination for a study, the agency's determination is final. Additional information may be
244 found in the *Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors -*
245 *Significant Risk and Nonsignificant Risk Medical Device Studies.*²⁶

246

247 Although not required by the regulations, FDA recommends that the IRB have written
248 procedures that explain how the IRB makes a SR/NSR determination.

249

²⁶ <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf>.