
Guidance for Industry

Protecting the Rights, Safety, and Welfare of Study Subjects - Supervisory Responsibilities of Investigators

DRAFT GUIDANCE

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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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1 **Guidance for Industry¹**
2 **Protecting the Rights, Safety, and Welfare of Study Subjects -**
3 **Supervisory Responsibilities of Investigators**
4

5
6 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
7 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
8 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
9 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
10 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
11 the appropriate number listed on the title page of this guidance.
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16 **I. INTRODUCTION**
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18 This guidance provides an overview of the responsibilities of a person who conducts a clinical
19 investigation of a drug, biologic, or medical device (an investigator as defined in 21 CFR
20 312.3(b) and 21 CFR 812.3(i)). The intent of this guidance is to help investigators meet their
21 responsibilities with respect to protecting human subjects and ensuring the integrity of the data
22 from clinical investigations. This guidance is also intended to clarify FDA's expectations
23 concerning the investigator's responsibility: (1) to supervise a clinical study in which some study
24 tasks are delegated to employees or colleagues of the investigator or other third parties, and (2)
25 to protect the rights, safety, and welfare of study subjects.
26

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

34 **II. OVERVIEW OF INVESTIGATOR RESPONSIBILITIES**
35

36 In conducting clinical investigations of drugs, including biological products, under 21 CFR part
37 312 and of medical devices under 21 CFR part 812, the investigator is responsible:

- 38 • for ensuring that a clinical investigation is conducted according to the signed investigator
39 statement for clinical investigations of drugs, including biological products, or agreement
40 for clinical investigations of medical devices, the investigational plan, and applicable
41 regulations;
- 42 • for protecting the rights, safety, and welfare of subjects under the investigator's care; and

¹ This guidance has been prepared by the Investigator Responsibilities Working Group, which includes representatives from the Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

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- for the control of drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100).

A. Clinical Trials of Drugs, Including Biological Products

An investigator's responsibilities in conducting clinical investigations of drugs or biologics under part 312 are stated in the regulations in that part. Many of these responsibilities are included in the required investigator's signed statement, Form FDA-1572 (see Attachment A) (hereinafter referred to as "1572"), in which the investigator makes the following commitments (see 21 CFR 312.53):

- To conduct the study(ies) in accordance with the relevant, current protocol(s) and to only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects;
- To personally conduct or supervise the described investigation(s);
- To inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met;
- To report to the sponsor adverse experiences that occur in the course of the investigations(s) in accordance with 21 CFR 312.64;
- That he/she has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug;
- To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments;
- To maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available to FDA for inspection in accordance with 21 CFR 312.68;
- That an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation;
- To promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others;
- To not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects;
- To comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR 312.

Note that although the 1572 specifically incorporates most of the requirements directed at investigators in part 312, there are additional requirements that are not listed in the 1572.

Investigators and sponsors should refer to 21 CFR Parts 50, 56, and 312 to ensure that they are familiar with all of FDA's requirements for the conduct of drug and biologics studies.

B. Device Trials

An investigator's responsibilities in conducting clinical investigations of a medical device under 21 CFR part 812 are stated in the regulations in that part, including the requirement that there be a signed agreement between the investigator and sponsor that includes a statement in which the investigator makes the following commitments (see 21 CFR 812.43(c)(4) and 812.100):

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- 91 • To conduct the investigation in accordance with:
- 92 – the signed agreement with the sponsor;
- 93 – the investigational plan;
- 94 – the regulations in 21 CFR part 812 and other applicable regulations; and
- 95 – any conditions of approval imposed by the reviewing IRB or FDA.
- 96 • To supervise all testing of the device involving human subjects (§ 812.43(c)(4)(ii))
- 97 • To ensure that the requirements for obtaining informed consent are met (§
- 98 812.43(c)(4)(iii) and § 812.100)
- 99

100 In addition to following the signed agreement, the investigator's responsibilities under part 812

101 are:

- 102 • To permit an investigational device to be used only with subjects under the investigator's
- 103 supervision and to supply an investigational device only to persons authorized to receive
- 104 it (§ 812.110(c))
- 105 • To return to the sponsor any remaining supply of the device or otherwise dispose of the
- 106 device as the sponsor directs upon completion or termination of a clinical investigation or
- 107 the investigator's part of an investigation (§ 812.110(e))
- 108 • To maintain accurate, complete, and current records relating to the investigator's
- 109 participation in an investigation (§ 812.140):
- 110 ○ All correspondence with another investigator, an IRB, the sponsor, a monitor, or
- 111 FDA, including required reports;
- 112 ○ Records of receipt, use or disposition of a device;
- 113 ○ Records of each subject's case history and exposure to the device;
- 114 ○ The protocol, with documents showing the dates of and reasons for each deviation
- 115 from the protocol, and
- 116 ○ Any other records that FDA requires to be maintained by regulation or by specific
- 117 requirement for a category of investigations or a particular investigation.
- 118 • To permit FDA to inspect and copy any records pertaining to the investigation including,
- 119 in certain situations, those which identify subjects (§ 812.145):
- 120 • To prepare and submit to the sponsor and, when required by regulation, the reviewing
- 121 IRB and monitor, the following complete, accurate, and timely reports (§ 812.150):
- 122 ○ Any *unanticipated adverse device effect* occurring during an investigation
- 123 ○ *Progress reports* on the investigation
- 124 ○ Any *deviation from the investigational plan* made to protect the life or physical
- 125 well-being of a subject in an emergency
- 126 ○ Any use of the device *without obtaining informed consent*
- 127 ○ A final report
- 128 ○ Any further information requested by FDA or the IRB about any aspect of the
- 129 investigation.
- 130

131 The medical device regulations do not require use of a specific form for an investigator's

132 statement and there are additional requirements that are not listed above (see Attachment B).

133 Investigators and sponsors should refer to 21 CFR Parts 50, 56, and 812 to ensure that they are

134 familiar with all of FDA's requirements for the conduct of device studies.

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136 Although the specific responsibilities for investigators in drug and biologic clinical trials are not
137 identical to the responsibilities for investigators in medical device clinical trials, the general
138 responsibilities are essentially the same. This guidance discusses certain of the general
139 responsibilities that are applicable to clinical trials of drugs, biologics, and medical devices.
140

141 Nothing in this guidance is intended to conflict with recommendations for investigators
142 contained in the International Conference on Harmonization Guidance for Industry, E6 Good
143 Clinical Practice: Consolidated Guidance (Good Clinical Practice Guidance”) (April 1996).
144 <http://www.fda.gov/cder/guidance/959fml.pdf>
145

III. CLARIFICATION OF CERTAIN INVESTIGATOR RESPONSIBILITIES

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148 This section of the guidance is intended to clarify the investigator’s responsibility: (1) to
149 supervise the conduct of the clinical investigation and (2) to protect the rights, safety, and
150 welfare of study participants in drug and medical device clinical trials.
151

A. Supervision of the Conduct of a Clinical Investigation

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154 As stated above, investigators who conduct clinical investigations of drugs, including
155 biological products, under 21 CFR Part 312 commit to personally conduct or supervise the
156 investigation. Investigators who conduct clinical investigations of medical devices, under 21
157 CFR Part 812 commit to supervise all testing of the device involving human subjects. It is
158 common practice for investigators to delegate certain study-related tasks to employees,
159 colleagues, or other third parties (individuals or entities not under the direct supervision of
160 the investigator). When tasks are delegated by the investigator, the investigator is
161 responsible for providing adequate supervision of those to whom tasks are delegated and the
162 investigator is accountable for regulatory violations resulting from failure to adequately
163 supervise the conduct of the clinical study.
164

165 In assessing the adequacy of supervision by an investigator, FDA focuses on four major
166 issues: (1) whether delegated individuals were qualified to perform such tasks, (2) whether
167 study staff received adequate training on how to conduct the delegated tasks and were
168 provided with an adequate understanding of the study, (3) whether there was adequate
169 supervision and involvement in the ongoing conduct of the study, and (4) whether there was
170 adequate supervision or oversight of any third parties involved in the conduct of a study to
171 the extent such supervision or oversight was reasonably possible.
172

1. What is Appropriate Delegation of Study-related Tasks?

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175 The investigator should ensure that any individual to whom a task is delegated is
176 qualified by education, training, and experience to perform the delegated task.
177 Appropriate delegation is primarily an issue for tasks that would be considered to be
178 clinical or medical in nature, such as evaluating study subjects to assess clinical response
179 to an investigational therapy (e.g., global assessment scales, vital signs) or providing part
180 of the medical care provided to subjects during the course of the study. Most
181 clinical/medical tasks require formal medical training and may also have licensing or
182 certification requirements. Such licensing requirements will vary from state to state.

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183 Clinical investigators should take such qualifications/licensing requirements into account
184 when considering to whom it would be appropriate to delegate specific tasks.
185

186 During inspections, FDA has identified instances in which study tasks have been
187 delegated to individuals lacking appropriate qualifications. Examples of inappropriate
188 delegation include:

- 189 • Screening evaluations, including obtaining medical histories and assessment of
190 inclusion/exclusion criteria, conducted by individuals with inadequate medical
191 training (e.g., a medical assistant)
- 192 • Physical examinations performed by unqualified personnel
- 193 • Evaluation of adverse events by individuals lacking appropriate medical
194 training, knowledge of the clinical protocol, and knowledge of the
195 investigational product
- 196 • Assessments of primary study endpoints (e.g., tumor response, global
197 assessment scales) by individuals lacking appropriate medical training and
198 knowledge of the protocol
- 199 • Informed consent obtained by individuals who lack the medical training,
200 knowledge of the clinical protocol, or familiarity of the investigational product
201 needed to be able to discuss the risks and benefits of a clinical trial with
202 prospective subjects
203

204 The investigator is responsible for conducting studies in accordance with the protocol
205 (see 21 CFR 312.60, Form FDA-1572, 21 CFR 812.43 and 812.100). Some protocols
206 specify the qualifications of the individuals who are to perform certain protocol-required
207 tasks, and these protocols must be followed even if state law permits differently qualified
208 people to perform the task. For example, even if the state in which the study site is
209 located permits nurse practitioners to perform physical examinations under the
210 supervision of a physician, if the protocol specifies that physical examinations must be
211 done by a physician, a physician must perform such exams.
212

213 The investigator should maintain a list of the appropriately qualified persons to whom
214 significant trial-related duties have been delegated.² This list should also describe the
215 delegated tasks, identify the training that individuals have received that qualifies them to
216 perform delegated tasks, and identify the dates of involvement in the study. An
217 investigator should maintain separate lists for each study conducted by the investigator.
218

219 *2. What is Adequate Training?*

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221 The clinical investigator should ensure that there is adequate training for all staff
222 participating in the conduct of the study. The investigator should specifically anticipate
223 the possibility of staff turnover during the conduct of the study (particularly if the study is
224 of long duration) and plan to ensure that there is adequate training of any replacement
225 staff. The investigator should ensure that staff:
226

- 227 • Have a general familiarity with the study and the protocol

² See Good Clinical Practice Guidance, section 4.1.5

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- Have a specific understanding of the details of the protocol and the investigational product, relevant to the tasks they will be performing
 - Are aware of regulatory requirements and acceptable standards for the conduct of clinical trials, both in respect to conduct of the clinical trial and human subject protection
 - Are competent to perform the tasks that they are delegated
 - Are informed of any pertinent changes during the conduct of the trial and educated or given additional training as appropriate

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If the sponsor provides training materials for investigators in the conduct of the study, the investigator should ensure that staff receives the sponsor's training, or information from the training, that is pertinent to their role in the study.

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3. *What is Adequate Supervision of the Conduct of an Ongoing Clinical Trial?*

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The investigator should have a detailed plan for the supervision and oversight of a clinical trial. Supervision and oversight should be provided even for individuals who are highly qualified and experienced. A plan might include the following elements, to the extent they apply to a particular trial:

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- Routine meetings with staff to review trial progress and update staff on any changes to the protocol or other procedures
 - Routine meetings with the sponsor's monitors
 - A procedure for correcting problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study
 - A procedure for documenting the performance of delegated tasks in a satisfactory manner and, where appropriate, verifying findings (e.g., observation of the performance of selected assessments or independent verification by repeating selected assessments)
 - A procedure for ensuring that the consent process is being conducted in accordance with 21 CFR Part 50 and that study subjects understand the nature of their participation, risks, etc.
 - A procedure for ensuring that information in source documents is accurately captured on the Case Report Forms
 - A procedure for dealing with data queries and discrepancies identified by the study monitor
 - Procedures for ensuring study staff comply with the protocol, adverse event assessment and reporting, and other medical issues that arise during the course of the study.

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The investigator should have sufficient time to properly conduct and supervise the clinical trial. The intensity of the supervision should be appropriate to the staff, the nature of the trial, and the subject population. In FDA's experience, the following factors may compromise the ability of an individual investigator to provide adequate supervision of the conduct of an ongoing clinical trial:

- Inexperienced study staff

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- 275 • Overburdened study staff
- 276 • Complex clinical trials (e.g., many observations, large amounts of data collected)
- 277 • Large number of subjects enrolled at a site
- 278 • A patient population that is quite sick
- 279 • Conducting a large number of studies concurrently
- 280 • Conducting a study from a remote (i.e., off-site) location;
- 281 • Conducting a study at multiple sites under the oversight of a single investigator,
- 282 particularly where those sites are not near each other (e.g., sites that are
- 283 geographically distant, in another city, county, state, or country).
- 284

285 It is preferable for any site with substantial enrollment to have an identified investigator
286 with clear responsibilities, but if that is not arranged, FDA believes there should
287 ordinarily be an individual responsible for the conduct of the clinical trial at each trial
288 site, identified as a subinvestigator. Subinvestigators should report directly to the
289 investigator (i.e., the clinical investigator should have clear responsibility for evaluating
290 the individual's performance and should have the authority to hire/fire the
291 subinvestigator).

292 4. *What are an Investigator's Responsibilities for Oversight of Other Parties* 293 *Involved in the Conduct of a Clinical Trial?*

294 a. Study staff not in the direct employ of the investigator

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297
298 The staff involved directly in the conduct of a clinical investigation may include
299 individuals who are not in the direct employ of the clinical investigator. For
300 example, a site management organization (SMO) may hire an investigator to
301 conduct a study and provide the investigator with a study coordinator or nursing
302 staff employed by the SMO. In this situation, the investigator should take steps to
303 assure that the staff not under his/her direct employ are qualified to perform
304 delegated tasks (see section III.A.1) and have received adequate training on
305 carrying out the delegated tasks and on the nature of the study (see section
306 III.A.2), or the investigator should provide such training. The investigator is
307 responsible for supervision of the study tasks performed by this staff, even though
308 they are not in his/her direct employ during the conduct of the study (see section
309 III.A.3) and this responsibility exists, no matter how qualified and experienced
310 these staff members are. In the event that the staff's performance of study-related
311 tasks is not adequate and cannot be made satisfactory by the investigator, the
312 investigator should document the observed deficiencies in writing to the staff's
313 supervisor(s). Depending on the severity of the deficiencies, the clinical trial may
314 need to be voluntarily suspended until personnel can be replaced.

315 b. Parties other than Study Staff

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318 There are often critical aspects of a study performed by parties not involved
319 directly in patient care or contact, and not under the direct control of the clinical
320 investigator. For example, clinical chemistry testing, radiologic assessments, and
321 electrocardiograms are commonly done by a central independent laboratory
322 retained by the sponsor or the investigator. Under these arrangements, the central

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323 laboratory usually provides the test results directly to the sponsor and to the
324 clinical investigator. Because the activities of these parties are critical to the
325 outcome of the study, and because the sponsor retains the services of the
326 laboratory, the sponsor is responsible for seeing that these parties are fulfilling
327 their responsibilities for the study.

328
329 Less frequently, a study may require that clinical investigators arrange to obtain
330 information critical to the study that cannot be obtained at the clinical
331 investigator's facility. For example, if the study protocol requires testing with
332 special equipment or expertise not available at the clinical investigator's facility,
333 the investigator might make arrangements for someone outside the facility to
334 perform the test. In this case, the results are provided directly to the clinical
335 investigator, who then submits the information to the sponsor. Where such
336 assessments are retained by the investigator, the investigator should take steps to
337 ensure that the facility is adequate (e.g., has the required certifications or
338 licenses). The investigator may also institute procedures to ensure the integrity of
339 data and records obtained from the party providing the information (e.g., a
340 process to ensure that records identified as coming from the party are authentic).
341 Procedures are particularly important when assessments are crucial to the
342 evaluation of the efficacy or safety of an intervention or to the decision to exclude
343 subjects who would be exposed to unreasonable risk.

344
345 Clinical investigators should carefully review the reports from these external
346 sources for results that are inconsistent with clinical presentation. To the extent
347 feasible, and considering the specifics of study design, the clinical investigator
348 should evaluate whether results appear reasonable, individually and in aggregate.
349 If clinical investigators detect possible errors or suspect that results from a central
350 laboratory might be questionable, the investigator should contact the sponsor
351 immediately.

c. Exception for Certain Device Studies

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355 In some cases, specialized expertise from a device sponsor is needed to perform
356 certain tasks. For example, when there is no one at the clinical site who can
357 program an investigational pacemaker, the expertise may be provided by the
358 sponsor's personnel, such as a field clinical engineer. The field clinical engineer
359 should be supervised by the sponsor and not by the clinical investigator. When a
360 field clinical engineer is designated by the sponsor to perform a specific activity
361 within the investigational plan, this activity should be described in the protocol.
362 The investigator retains responsibility for ensuring that the protocol is followed.

B. Protecting the Rights, Safety, and Welfare of Study Subjects

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367 Clinical investigators are responsible for protecting the rights, safety, and welfare of subjects
368 under their care during a clinical trial (21 CFR 312.60 and 812.100). The clinical
369 investigator should provide a reasonable standard of medical care for study subjects for
370 medical problems arising during participation in the trial that are, or could be related, to the

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371 study intervention. The investigator should be readily available to provide such care during
372 the study or should assure that other identified, qualified individual(s) are available to
373 provide such care. Failure to adhere to the protocol can expose subjects to unreasonable
374 risks.

1. Reasonable Medical Care Necessitated by Participation in a Clinical Trial

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378 During and following a subject's participation in a trial, the investigator should ensure
379 that adequate medical care is provided to a subject for any adverse events, including
380 clinically significant laboratory values, related to the trial. The investigator should
381 inform a subject when medical care is needed for intercurrent illness(es). The
382 investigator should inform the subject's primary physician about the subject's
383 participation in the trial if the subject has a primary physician and if the subject agrees to
384 the primary physician being informed.

385
386 If the investigator does not possess the necessary skills to provide adequate medical care
387 for the subject, the investigator should make every effort to obtain appropriate care. For
388 example, if a carotid stent is placed in a subject by an interventional neuroradiologist and
389 the subject suffers a cerebral stroke, the neuroradiologist should assess the clinical status
390 of the subject and transfer the subject to a neurology service. Subjects should receive
391 appropriate medical evaluation and treatment until resolution of any condition related to
392 the study intervention that develops during the course of their participation in a study,
393 even if the follow-up period extends beyond the end of the study at the investigative site.

2. Reasonable Access to Medical Care

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395
396
397 To protect subjects from unnecessary risks, clinical investigators should be available to
398 subjects during the conduct of the trial at their site. Availability is particularly important
399 where subjects are receiving a drug that has significant toxicity or abuse potential. For
400 example, if a study drug has potentially fatal toxicity, the investigator should be readily
401 available by phone or other electronic communication, and in reasonably close proximity
402 to study subjects (e.g., not in another state or on prolonged travel). Study subjects should
403 be clearly educated on the possible need for such contact and on precisely how to obtain
404 it, generally by providing pertinent phone numbers, websites, etc., in writing. Prior to
405 undertaking the conduct of a study, prospective investigators should consider whether
406 they can be available to the extent needed given the nature of the trial.

407
408 If the investigator is not going to be available for some period during the study, clinical
409 responsibility for study subjects should be delegated to a specific qualified physician who
410 will be readily available to subjects. This delegation should be documented in a 1572 or
411 investigator agreement (the physician should be listed as a subinvestigator) and also
412 submitted to the IRB for review (as a change in the research activity requiring IRB
413 review under 21 CFR 56.108(a)). If the clinical investigator is a non-physician, the
414 investigator should make adequate provision for any necessary medical care that the
415 investigator is not qualified to provide.

3. Protocol Violations that Present Unreasonable Risks

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419 There are occasions when a failure to adhere to the protocol may be considered a failure
420 to protect the rights, safety, and welfare of subjects. For example, failure to adhere to
421 inclusion/exclusion criteria that are specifically intended to exclude subjects for whom
422 the study drug or device poses unreasonable risks (e.g., enrolling a subject with decreased
423 renal function in a trial in which decreased function is exclusionary because the drug may
424 be nephrotoxic) may be considered failure to protect the rights, safety, and welfare of the
425 enrolled subject. Similarly, failure to perform safety assessments intended to detect drug
426 toxicity within protocol-specified time frames (e.g., CBC for an oncology therapy that
427 causes neutropenia) may be considered failure to protect the rights, safety, and welfare of
428 the enrolled subject. Investigators should seek to minimize such risks by adhering
429 closely to the study protocol.

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Attachment A

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<p>DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION STATEMENT OF INVESTIGATOR (TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312) (See instructions on reverse side.)</p>	<p>Form Approved: OMB No. 0910-0014. Expiration Date: January 31, 2006. See OMB Statement on Reverse.</p>
<p>NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).</p>	
<p>1. NAME AND ADDRESS OF INVESTIGATOR</p>	
<p>2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.</p> <p><input checked="" type="checkbox"/> CURRICULUM VITAE <input type="checkbox"/> OTHER STATEMENT OF QUALIFICATIONS</p>	
<p>3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.</p>	
<p>4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.</p>	
<p>5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).</p>	
<p>6. NAME S OF THE SUBINVESTIGATORS (e.g., research fellows, residents, associates) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).</p>	
<p>7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.</p>	

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8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

- FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.
- FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

- I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct or supervise the described investigation(s).
- I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
- I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
- I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

**INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:**

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR

11. DATE

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

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Attachment B

**INVESTIGATORS' RESPONSIBILITIES
FOR SIGNIFICANT RISK DEVICE INVESTIGATIONS**

This document is intended to assist investigators in identifying and complying with their responsibilities in connection with the conduct of clinical investigations involving medical devices. Although this guidance primarily addresses duties imposed upon clinical investigators by regulations of the Food and Drug Administration (FDA), investigators should be cognizant of additional responsibilities that may derive from other sources (such as the study protocol itself, the investigator agreement, any conditions of approval imposed by FDA or the governing Institutional Review Board, as well as institutional policy and state law).

GENERAL RESPONSIBILITIES OF INVESTIGATORS (21 CFR 812.100)

1. Ensuring that the investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations.
2. Protecting the rights, safety, and welfare of subjects under the investigator's care.
3. Controlling devices under investigation.
4. Ensuring that informed consent is obtained from each subject in accordance with 21 CFR Part 50, and that the study is not commenced until FDA and IRB approvals have been obtained.

SPECIFIC RESPONSIBILITIES OF INVESTIGATORS (21 CFR 812.110)

1. Awaiting IRB approval and any necessary FDA approval before requesting written informed consent or permitting subject participation.
2. Conducting the investigation in accordance with:
 - a. the signed agreement with the sponsor;
 - b. the investigational plan;
 - c. the regulations set forth in 21 CFR Part 812 and all other applicable FDA regulations; and
 - d. any conditions of approval imposed by an IRB or FDA.

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- 474 3. Supervising the use of the investigational device. An investigator shall permit an
475 investigational device to be used only with subjects under the investigator's supervision.
476 An investigator shall not supply an investigational device to any person not authorized
477 under 21 CFR Part 812 to receive it.
478
- 479 4. Disposing of the device properly. Upon completion or termination of a clinical
480 investigation or the investigator's part of an investigation, or at the sponsor's request, an
481 investigator shall return to the sponsor any remaining supply of the device or otherwise
482 dispose of the device as the sponsor directs.
483

MAINTAINING RECORDS (21 CFR 812.140)

484 An investigator shall maintain the following accurate, complete, and current records relating to
485 the investigator's participation in an investigation:
486

- 487
- 488
- 489 1. Correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA.
490
- 491 2. Records of receipt, use or disposition of a device that relate to:
492 a. the type and quantity of the device, dates of receipt, and batch numbers or code
493 marks;
494 b. names of all persons who received, used, or disposed of each device;
495 c. the number of units of the device returned to the sponsor, repaired, or otherwise
496 disposed of, and the reason(s) therefore.
497
- 498 3. Records of each subject's case history and exposure to the device, including:
499 a. documents evidencing informed consent and, for any use of a device by the
500 investigator without informed consent, any written concurrence of a licensed
501 physician and a brief description of the circumstances justifying the failure to
502 obtain informed consent;
503 b. all relevant observations, including records concerning adverse device effects
504 (whether anticipated or not), information and data on the condition of each subject
505 upon entering, and during the course of, the investigation, including information
506 about relevant previous medical history and the results of all diagnostic tests;
507 c. a record of the exposure of each subject to the investigational device, including
508 the date and time of each use, and any other therapy.
509
- 510 4. The protocol, with documents showing the dates of and reasons for each deviation from
511 the protocol.
512
- 513 5. Any other records that FDA requires to be maintained by regulation or by specific
514 requirement for a category of investigations or a particular investigation.
515
516

INSPECTIONS (21 CFR 812.145)

517
518
519 Investigators are required to permit FDA to inspect and copy any records pertaining to the
520 investigation including, in certain situations, those which identify subjects.
521

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SUBMITTING REPORTS (21 CFR 812.150)

522 An investigator shall prepare and submit the following complete, accurate, and timely reports:
523

524 1. To the sponsor and the IRB:

526 -Any *unanticipated adverse device effect* occurring during an investigation. (Due
527 no later than 10 working days after the investigator first learns of the effect.)

528 -*Progress reports* on the investigation. (These reports must be provided at regular
529 intervals, but in no event less often than yearly. If there is a study monitor, a copy
530 of the report should also be sent to the monitor.)

531 -Any *deviation from the investigational plan* made to protect the life or physical
532 well-being of a subject in an emergency. (Report is due as soon as possible but no
533 later than 5 working days after the emergency occurs. Except in emergency
534 situations, a protocol deviation requires prior sponsor approval; and if the
535 deviation may affect the scientific soundness of the plan or the rights, safety, or
536 welfare of subjects, prior FDA and IRB approval are required.)

537 -Any use of the device *without obtaining informed consent*. (Due within 5
538 working days after such use.)

539 -A *final report*. (Due within 3 months following termination or completion of the
540 investigation or the investigator's part of the investigation. For additional
541 guidance, see the discussion under the section entitled "Annual Progress Reports
542 and Final Reports.")

543 -Any *further information* requested by FDA or the
544 IRB about any aspect of the investigation.

545
546 2. To the Sponsor:
547 -*Withdrawal of IRB approval* of the investigator's part of an investigation. (Due
548 within 5 working days of such action).

549

550

551

INVESTIGATIONAL DEVICE DISTRIBUTION AND TRACKING

552

553

554 The IDE regulations prohibit an investigator from providing an investigational device to any
555 person not authorized to receive it (21 CFR 812.110(c)). The best strategy for reducing the risk
556 that an investigational device could be improperly dispensed (whether purposely or
557 inadvertently) is for the sponsor and the investigators to closely monitor the shipping, use, and
558 final disposal of the device(s). Upon completion or termination of a clinical investigation (or the
559 investigator's part of an investigation), or at the sponsor's request, an investigator is required to
560 return to the sponsor any remaining supply of the device or otherwise to dispose of the device as
561 the sponsor directs (21 CFR 812.110(c)). Investigators must also maintain complete, current and
562 accurate records of the receipt, use, or disposition of investigational devices (21 CFR
563 812.140(a)(2)). Specific recordkeeping requirements are set forth at 21 CFR 812.140(a).

564

PROHIBITION OF PROMOTION AND OTHER PRACTICES (21 CFR

566 **812.7)**

567

568 The IDE regulations prohibit the promotion and commercialization of a device that has not been
569 first cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and

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570 investigators (or any person acting on behalf of a sponsor or investigator), and encompasses the
571 following activities:

- 572
- 573 1. Promotion or test marketing of the investigational device;
 - 574
 - 575 2. Charging subjects or investigators for the device a price larger than is necessary to
576 recover the costs of manufacture, research, development, and handling;
 - 577
 - 578 3. Prolonging an investigation beyond the point needed to collect data required to determine
579 whether the device is safe and effective; and,
 - 580
 - 581 4. Representing that the device is safe or effective for the purposes for which it is being
582 investigated.