Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs

Frequently Asked Questions – Statement of Investigator (Form FDA 1572)

DRAFT GUIDANCE

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Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs Frequently Asked Questions-Statement of Investigator (Form FDA 1572)

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Information Sheet Guidance For Sponsors, Clinical Investigators, and IRBs[1] Frequently Asked Questions Statement of Investigator (Form FDA 1572)

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

This guidance is intended to assist sponsors, institutions, institutional review boards (IRBs) and clinical investigators involved in clinical investigations of investigational drugs and biologics. This guidance applies to clinical investigations conducted under 21 CFR Part 312 (Investigational New Drug Applications or IND regulations). It describes how to complete the Statement of Investigator form (Form FDA 1572).

The Food and Drug Administration (FDA or agency) has received a number of questions about the Form FDA 1572. The most frequently asked questions are answered below. If you do not see your question answered here, you may submit it to gcp.questions@fda.hhs.gov or druginfo@fda.hhhs.gov.

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

I. General Questions

1. What is the Statement of Investigator, Form FDA 1572?

The Statement of Investigator, Form FDA 1572 (1572), is an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic. The most recent version of the 1572 is available online at www.fda.gov/opacom/morechoices/fdaforms/cder.html.

[1] This guidance document was developed by the Good Clinical Practice Program in coordination with the Agency's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.

2. Why does this form need to be completed by an investigator?

The 1572 has two purposes: 1) to provide the sponsor with information about the investigator's qualifications and the clinical site that will enable the sponsor to establish and document that the investigator is qualified and the site is an appropriate location at which to conduct the study, and; 2) to inform the investigator of his/her obligations and obtain the investigator's commitment to follow pertinent FDA regulations. Investigators should complete the form as accurately as they can. Investigators should be aware that making a willfully false statement is a criminal offense under 18 U.S.C. 1001. Further, submission of a deliberately false statement to the sponsor or to the agency can be taken into consideration in a disqualification proceeding.

3. When must this form be completed and signed by an investigator?

The sponsor must obtain a completed and signed 1572 before permitting an investigator to begin participation in a clinical study (21 CFR 312.53(c)). The investigator should sign the form only after being given enough information to be informed about the study and to understand the commitments described in Block # 9 of the 1572. Having enough information about the study typically means that the investigator has received copies of, has read, and understands the investigator's brochure and the study protocol, and is familiar with the regulations governing the conduct of clinical studies.

The investigator's signature on this form constitutes the investigator's affirmative assertion that he or she is qualified to conduct the study and constitutes the investigator's commitment to abide by FDA regulations in the conduct of the study.

4. Must the investigator be a physician?

The regulations do not require that the investigator be a physician. Sponsors are required to select only investigators qualified by training and experience as appropriate experts to investigate the drug (21 CFR 312.53(a)). In the event the clinical investigator is a non-physician, a qualified physician (or dentist, when appropriate) should be listed as a subinvestigator for the trial and should be responsible for all trial-related medical (or dental) decisions (ICH E6 Section 4.3.1; http://www.fda.gov/cder/guidance/959fnl.pdf).

5. What are the minimum qualifications of an investigator?

As stated in #4, the regulations require that sponsors select investigators who are qualified by training and experience as appropriate experts to investigate the drug. The regulations do not specify the minimum requirements nor do the regulations specify what qualifications an investigator must have in order to be considered qualified by training and experience to conduct a study. Sponsors have discretion in determining what qualifications will be needed, based on the general recognition that this would include familiarity with human subject protection (HSP) requirements and practices as well as good clinical practice (GCP) standards for the conduct of clinical studies.

6. Does the 1572 need to be submitted to FDA?

No. Although the sponsor is required to collect the 1572 from the investigator, FDA does not require the form to be submitted to the agency. Many sponsors submit the 1572 to FDA, however, because it collects, in one place, information that must be submitted to FDA under 21 CFR 312.23(a)(6)(iii)(b).

7. When must a 1572 be updated or a new 1572 completed and signed by the investigator to reflect new or changed information?

If there are changes to information contained on the 1572 (e.g., an IRB address change, the addition of new subinvestigators, discontinuing the use of a clinical lab), the investigator should document the changes in the study records and inform the sponsor of these changes, so that the sponsor can appropriately update the IND. The 1572 itself does not need to be revised and a new 1572 need not be completed and signed by the investigator

8. If a clinical investigation is not conducted under an IND or is for a medical device, must investigators sign a 1572?

No. Under the regulations, a 1572 is only required for studies of investigational drugs and biologics conducted under an IND. It is not required for studies that are not done under an IND, and is not applicable to investigational device studies. Sponsors of device studies must obtain a signed agreement (containing information similar to that requested on the 1572) from each participating investigator, per 21 CFR 812.43(c) (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.43).

9. Must a sponsor conduct a foreign clinical study under an IND?

No. A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived (see Question 11 below). When the foreign clinical study is not conducted under an IND, the sponsor must ensure that this study complies with 21 CFR 312.120 "Foreign clinical studies not conducted under an IND" if the sponsor intends to submit the study to FDA to support clinical investigations conducted in the United States and/or marketing approval. An application based solely on foreign clinical study data must meet criteria listed in 21 CFR 314.106.

10. Must investigators who conduct studies outside of the United States sign a 1572?[2]

If a foreign clinical study is conducted under an IND, then all FDA IND regulations, including the requirement to obtain a signed 1572, must be met. If a study is conducted outside of the U.S. and is not conducted under an IND, then the investigator need not sign a 1572.

11. For foreign clinical studies conducted under an IND, how can an investigator sign the 1572 when the investigator knows he/she cannot commit to all of the requirements on the form, specifically IRB membership (21 CFR 56.107)?

[2] Investigators conducting studies outside of the U.S. may want to consult with local regulatory authorities for additional guidance when considering whether to conduct studies under a U.S. IND.

IRB review and approval is required before a study can be initiated under an IND [21 CFR 56.103(a)]. FDA may waive any of the IRB requirements for specific research activities or for classes of research activities otherwise covered by the IRB regulations [21 CFR 56.105], but FDA uses the waiver provision only when alternative mechanisms for ensuring protection of the rights and welfare of human subjects are acceptable. The most common circumstance for which FDA receives a waiver request is when a sponsor wishes to conduct a foreign clinical study under an IND. In this case, typically an Independent Ethics Committee (IEC) that operates in accordance with Good Clinical Practice (GCP) is utilized instead of a U.S. IRB. Although its membership and functions for assuring human subject protection are comparable to an IRB, an IEC may not meet all of the IRB requirements contained in 21 CFR Part 56.

For foreign studies, an IRB waiver request should contain a description of alternative mechanisms for assuring human subject protection. It would generally be acceptable for a waiver request to state the intention to use an IEC that complies with GCP (e.g., ICH E6) instead of an IRB that complies with 21 CFR Part 56.

The sponsor should submit the waiver request to the IND under which the study will be conducted. The IND will have been submitted to the appropriate review division in either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER).

The sponsor will be informed by the agency in writing whether the waiver request is denied or granted. If a waiver is granted, the sponsor should have investigators attach a copy of the letter granting the waiver to the signed 1572 in the investigator's record.

12. Must foreign clinical sites in a multinational study that includes domestic sites be conducted under an IND?

No. A multinational study may be comprised of several protocols, some of which are conducted under an IND and others which are not. Investigational drug and biologics studies conducted in the U.S. must be conducted in compliance with the IND requirements contained in 21 CFR 312, which includes the requirement that investigators sign the 1572. If a study also involves foreign clinical sites, the sponsor may choose, but is not required, to include the foreign clinical sites under the IND. The U.S. sites and any foreign sites included under the IND must follow the protocol that was submitted to the IND and these investigators would be required to sign the 1572. For foreign sites that are not included under the IND, the protocol does not need to be submitted to the IND, and investigators from these foreign sites are not required to sign the 1572. If the intent is to pool the data from U.S. and foreign sites, the protocols would ordinarily be very similar or identical. We recommend that the sponsor discuss plans to pool U.S. and foreign sites with the appropriate FDA review division if the sponsor intends to submit the data from these studies in an application for marketing approval.

Note however, that 21 CFR 312.32(b) requires sponsors to promptly review information about the safety of the investigational drug obtained or otherwise received by the sponsor from any source, foreign or domestic. Under 21 CFR 312.32(c), sponsors must also notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected. This means that FDA and all

participating investigators under the IND would be informed of such an adverse experience, even if it occurred in a foreign trial not conducted under the IND.

13. How does a sponsor submit information to FDA about a foreign clinical study that was not conducted under an IND?

Under 21 CFR 312.120, the sponsor can submit information to FDA about a foreign clinical study that was not conducted under an IND when the study is to be utilized to support clinical investigations in the United States and/or marketing approval. When submitting information about a foreign study, it is helpful to clearly identify in the cover letter that the material is being submitted in accordance with 21 CFR 312.120. Specific instructions on how and what to submit to the agency can be found at 21 CFR 312.120(b).

14. Should a new form be prepared and signed when the OMB expiration date is reached?

No. There is no need to prepare and sign a new 1572 when the OMB expiration date has been reached. The date on the form refers to the Office of Management and Budget's time frame during which FDA may collect information contained in this form.

15. Does FDA expect a double-sided 1572, or is a two-page document printed from the FDA website acceptable?

Either is acceptable; however, FDA recommends that a two-page document be stapled so that there is no question about what form the investigator signed.

16. Is a handwritten form acceptable?

Although the form may be completed by hand, printed copies of the 1572 should be used.

II. Block #1: Name and Address of Investigator

17. How should an investigator's name appear on the 1572?

Block #1 should contain the investigator's legal name.

18. What address should be entered into Block #1?

The investigator's official address of record should be entered in Block #1 of the 1572.

19. Should co-investigators be listed on the 1572 in Block #1? Is it acceptable to have two investigators?

Co-investigators should not be listed in Block #1. The term co-investigator is not defined in FDA regulations. As commonly used, the term is meant to indicate that each co-investigator is fully responsible for fulfilling all of the obligations of an investigator as identified in 21 CFR 312.60. Thus under 21 CFR 312.3(b), each co-investigator is an investigator, and as such must sign a separate 1572. It is acceptable to have more than one investigator at a particular site. This is distinct from a subinvestigator (see #30) whose role in the study is more limited.

III. Block #2: Curriculum Vitae (CV)/Statement of Qualifications

20. What is the purpose of Block #2?

Block #2 requires the investigator to attach a curriculum vitae (CV) or other statement of qualifications, showing the education, training and experience that qualifies the investigator as an expert in the clinical investigation of the drug/biologic for the use under investigation. Information identified in this block and attached to the 1572 enables the sponsor to assess an investigator's qualifications.

21. Does the CV or other statement of qualifications need to be updated during a study?

No. FDA regulations do not require a CV or other statement of qualifications to be updated during a study.

22. Are CVs required to be signed and dated?

No. FDA regulations do not require a CV to be signed and dated. The investigator's signature on the 1572 is sufficient to attest to the accuracy of the CV or other statement of qualifications submitted with the 1572.

IV. Block #3: Research Facilities

23. What address(es) should be entered in Block #3?

The address(es) of the location(s) where the investigation will be conducted and where the test articles will be shipped, if different from the investigator's address of record, should be entered in Block #3.

24. What qualifies as a research facility for Block #3?

Block #3 is intended to identify facilities where study activities will be conducted and study data will be generated or collected. This includes facilities where subjects will be seen and study procedures performed (for example, the location where the test article will be administered, or where physical exams will be performed). Facilities where other important study functions are performed may also be identified in Block #3 (for example, a research laboratory where the test article is prepared or a special storage facility where the test article will be kept).

25. If an investigator sees study subjects at more than one site, should the investigator list all sites on the 1572?

Yes. The names and addresses of each of the study sites should be identified in Block #3.

26. As a convenience for study subjects, the protocol allows for daily injections to be administered by a registered nurse at each subject's home. Do subjects' home addresses need to be listed in Block #3?

No. Subjects' home addresses do not have to be listed on the 1572. Study records should reflect that the test article was administered at subjects' homes per the protocol.

V. Block #4: Name and Address of Clinical Laboratory Facilities

27. What qualifies as a clinical laboratory facility for Block #4?

Block #4 is intended to identify clinical laboratories or testing facilities directly contributing to or supporting the clinical trial (for example, diagnostic labs performing blood work, imaging centers, cardiology labs, etc.).

28. If a central laboratory is sending samples to its own satellite labs for additional testing, should the satellite labs be identified in Block #4?

It is only necessary to list the central laboratory, provided that the central laboratory can trace the samples to the satellite labs where the tests were performed.

VI. Block #5: Name and address of the Institutional Review Board responsible for the review and approval of the study(ies)

29. Does the IRB reviewing and approving the study have to be at the same location as where the research is conducted?

The regulations permit review of research by IRBs in locations other than where the research is being performed (e.g. independent or non-institutional IRB; use of a cooperative IRB review process; see 21 CFR 56.114). Therefore an IRB may review studies that are not performed on-site as long as requirements in 21 CFR Parts 50 and 56 are met.

VII. Block #6: Names of the subinvestigators who will be assisting the investigator in the conduct of the investigations

30. Who should be listed as a subinvestigator in Block #6?

FDA's regulation at 21 CFR 312.3(b) states: "In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 'Subinvestigator' includes any other individual member of that team." 21 CFR 312.53(c)(1)(viii) requires the investigator to provide "A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s)."

The purpose of Block #6 is to capture information about individuals who, as part of an investigative team, will be assisting the investigator and who make a direct and significant contribution to the data. The decision to list an individual in Block #6 depends on his/her level of responsibility (i.e., whether he/she is performing significant study-related duties). In general, if an individual is directly involved in the treatment or evaluation of research subjects, that person should be listed on the 1572. For example, as part of the protocol of a clinical investigation, if each subject needs to visit a specified internist who will perform a full physical to qualify subjects for the study, that internist should be listed in Block #6.

31. *Should research nurses, other nurses, residents, fellows, office staff, or other hospital staff be listed in Block #6?*

Hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care but who do not make a direct and significant contribution to the data do not need to be listed individually. It is not necessary to include in this block a person with only an occasional role in the conduct of the research, e.g., an on-call physician who temporarily dealt with a possible adverse effect or a temporary substitute for any research staff (ICH E3 Section 6; http://www.fda.gov/cder/guidance/iche3.pdf).

If a number of staff residents on rotation participate in the study, a general statement regarding their planned participation may be included in Block #6.

32. Should pharmacists or research coordinators be listed in Block #6?

If a pharmacist is merely dispensing tablets and has no responsibility for preparing the test article(s) or evaluating or reporting data relative to the study activities, then it is not necessary to list the pharmacist. On the other hand, if the pharmacist will be compounding, labeling, monitoring and reporting test article compliance data, it would be appropriate to list the pharmacist in Block # 6.

If a research coordinator is performing critical study functions and collecting and evaluating study data, the coordinator should be listed in Block #6. If the research coordinator is only transcribing data and maintaining study files, the coordinator does not need to be listed.

33. Is a statement of qualifications required for subinvestigators?

No. The regulations at 21 CFR 312.53(c) (1)(viii) only require their names to be listed in Block #6 of the 1572.

34. Do individuals who are listed in Block #6 on the 1572 have to submit information about their financial interests?

Yes. Under 21 CFR Part 54 (Disclosure of Financial Interests by Clinical Investigators), a person listed or identified as an investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects must submit financial disclosure information to the sponsor. For purposes of this financial disclosure regulation, the term investigator also includes the spouse and each dependent child of the investigator and subinvestigator. (21 CFR 54.2(d) and 54.4).

As further explained in the FDA Guidance for Industry Financial Disclosure by Clinical Investigators (http://www.fda.gov/oc/guidance/financialdis.html), for drugs and biological products, clinical investigator means the individual(s) who actually conduct(s) and take(s) responsibility for an investigation, i.e., under whose immediate direction the drug or biologic is administered or dispensed to a subject or who is directly involved in the evaluation of research subjects. Where an investigation is directed by more than one person at a site, there may be more than one investigator who must report. The terms investigators and subinvestigators include persons who fit any of these criteria: sign the Form FDA 1572, are identified as an investigator in

initial submissions or protocol amendments under an IND, or are identified as an investigator in the NDA/BLA. For studies not conducted under an IND, the sponsor will need to identify in Form FDA 3454 and/or Form FDA 3455 the names of investigators and subinvestigators they consider covered by 21 CFR Part 54. We expect that there will be at least one such person at each clinical site. If, however, there are other persons who are responsible for a study at a site, those persons should also be included as investigators.

The definition of "clinical investigator" in 21 CFR Part 54 is intended to identify the individuals who should be considered investigators for purposes of reporting under the rule, generally, the people taking responsibility for the study at a given study site. For drugs, biological products and devices, it should be noted that hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care, but who do not make direct and significant contribution to the data, are not meant to be included under the definition of clinical investigator.