Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs

Frequently Asked Questions Statement of Investigator (Form FDA 1572) (Revision 1)

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Paul Gouge, 301-796-3093, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice (OGCP)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

This guidance is intended to assist sponsors, clinical investigators, and institutional review boards (IRBs) involved in clinical investigations of investigational drugs and biological products. This guidance applies to clinical investigations conducted under 21 CFR part 312 (investigational new drug application (IND) regulations) and describes how to complete the Statement of Investigator (Form FDA 1572).

II. BACKGROUND

FDA has received questions about Form FDA 1572. The most frequently asked questions (FAQs) are answered in the information sheet guidance for sponsors, clinical investigators, and IRBs *Frequently Asked Questions—Statement of Investigator (Form FDA 1572)* (May 2010)[2] (the Form FDA 1572 FAQ Guidance).

This guidance, when finalized, partially revises the Form FDA 1572 FAQ Guidance and answers additional questions received by FDA. Questions not answered either in this guidance or in the Form FDA 1572 FAQ Guidance may be submitted to druginfo@fda.hhs.gov.

This guidance has been developed in response to multiple inquiries regarding waivers of the signature requirement on Form FDA 1572 and, when finalized, will explain FDA's current

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Office of Good Clinical Practice at the Food and Drug Administration.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

thinking regarding signature waivers. Specifically, this draft guidance revises general questions 10, 11, and 13 from the Form FDA 1572 FAQ Guidance and includes a new section (see questions 39 through 46) about waivers of the Form FDA 1572 signature requirement.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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.

III. GENERAL QUESTIONS (10, 11, AND 13)

10. Must investigators who conduct studies outside of the United States sign a 1572? [Revised 2021]

If a clinical study is conducted at a foreign site under an IND, all FDA IND regulations, including the requirement to obtain a signed 1572 (21 CFR 312.53(c)(1)), must be met unless the sponsor requests and is granted a waiver that provides for specific exceptions. In the case where a foreign investigator cannot or will not sign Form FDA 1572 (e.g., because regional, national, or local laws or regulations prohibit its signing), the sponsor may submit a request for a waiver of the 1572 signature requirement under 21 CFR 312.10 (see section [IV] of this guidance); alternatively, the site may operate as a non-IND site, in which case the study would be conducted as a non-IND study.

If a clinical study is conducted outside of the United States and the study is not under an IND, then the investigator need not sign a 1572. If the study data from a non-IND site is to be submitted to support a marketing application (e.g., a new drug application (NDA)), the study at the non-IND site must be conducted in compliance with 21 CFR 312.120. (Also, see question 14 in the Form FDA 1572 FAQ Guidance.)

11. If a foreign clinical study is being conducted under an IND, what are the investigator's responsibilities with respect to regional, national, or local laws and regulations? [Revised 2021]

Investigators are responsible for complying with the applicable laws and regulations of the country in which the study is being conducted, regardless of whether the study is being conducted under an IND. We recommend that sponsors obtain signed, written statements from investigators acknowledging their commitment to comply with regional, national, or local laws and requirements. In addition, if a foreign clinical study is being conducted under an IND, the investigator must sign Form FDA 1572 (investigator statement) (21 CFR 312.53(c)(1)) and ensure that the study is conducted in accordance with the investigator statement and all other applicable regulations under 21 CFR part 312 unless the sponsor has requested, and FDA has granted, a waiver of the signature requirement. If a waiver is granted, the sponsor and

investigator must ensure that the study is conducted in accordance with the terms of the waiver. (See section [IV] of this guidance.)

13. If a sponsor chooses to conduct a foreign clinical study (or operate non-U.S. sites in a multinational study) under an IND and the investigators at these non-U.S. sites follow the recommendations in the ICH E6 Good Clinical Practice Consolidated Guidance,[3] would the non-U.S. investigators also be in compliance with FDA's IND requirements under 21 CFR part 312?
[Revised 2021]

Yes, with three exceptions.

The first exception is that the FDA requirements for IRBs under 21 CFR part 56 are slightly different than ICH E6 with respect to membership and function. To address this issue, as described in question 12,[4] the sponsor can request that FDA provide a specific waiver from the part 56 IRB requirements, allowing an IEC that complies with good clinical practice to substitute for the IRB.[5]

The second exception is that the requirements for informed consent under 21 CFR part 50 for particular clinical trials (e.g., emergency research under 21 CFR 50.24, clinical investigations involving pediatric subjects under subpart D) are more extensive than ICH E6 with respect to IRB responsibilities. Our experience has not revealed that this difference has caused a conflict, but in the event of one, we would be willing to discuss a resolution with the sponsor on a case-by-case basis.

The third exception is that ICH E6 does not require investigators to sign a Form FDA 1572. To address this issue, the sponsor can request a specific waiver of the signature requirement on Form FDA 1572 pursuant to 21 CFR 312.10. (See section [IV] of this guidance.)

If the investigator or sponsor concludes that there are other conflicting requirements, the sponsor may request a waiver from FDA from the specific requirement under 21 CFR 312.10.

[3] Throughout this guidance, ICH E6 refers to ICH guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (February 2018).

[4] See question 12 in the information sheet guidance for sponsors, clinical investigators, and IRBs*; Frequently Asked Questions—Statement of Investigator (Form FDA 1572)*.

[5] See the information sheet guidance for sponsors, clinical investigators, and IRBs *Waiver of IRB Requirements for Drug and Biological Product Studies* (January 2006).

IV. SECTION #9–11: COCOMMITMENTS, DATE, AND SIGNATURE OF INVESTIGATOR — WAIVER OF SIGNATURE ON FORM FDA 1572

39. ***A sponsor may encounter situations in which investigators in foreign countries cannot or will not sign Form FDA 1572, yet the sponsor wishes to conduct the study at these sites under an IND. What can a sponsor do?***
[New 2021]

Under FDA regulations, sponsors may submit requests to FDA for a waiver of an IND requirement (21 CFR 312.10). Such submissions may include request for a waiver of the requirement that sponsors obtain an investigator signature on Form FDA 1572 (21 CFR 312.53 (c)(1)). Waiver of the signature on Form FDA 1572, when granted, enables the study at foreign sites to be and/or remain under an IND even though the investigator at those foreign sites cannot or will not sign Form FDA 1572, provided that the sponsor complies with the terms of the waiver. (See below for further information regarding the waiver process and commitments.)

40. ***What should a sponsor submit to the IND when requesting a waiver of the 1572 signature requirement?***
[New 2021]

1. A clear statement that the sponsor is requesting a waiver of the signature requirement on the 1572

2. The study title, protocol number, study sites, and investigator name(s) that would be subject to the waiver (Note: If multiple sites are identified, the submission should identify which investigator(s) is associated with each site.)

A waiver request is required to contain at least one of the following (21 CFR 312.10(a)):

3. The reason(s) each investigator cannot or will not sign Form FDA 1572

4. The sponsor's proposed alternative course of action to adequately satisfy the purpose of a signed Form FDA 1572

5. Other information justifying a waiver

For FDA to consider granting the waiver request, it is important that the request addresses all of the items above.

41. ***What documentation should a sponsor submit to show that they have an acceptable alternative course of action to satisfy the purpose of a signed Form FDA 1572? Can you provide an example?***
[New 2021]

There may be multiple ways for a sponsor to assure FDA that its alternative course of action adequately satisfies the purpose of a signed Form FDA 1572. Although there may be other approaches, FDA recommends using the example and suggested templates found in the Appendix of this guidance, which will likely result in the most efficient review of the waiver request.

An alternative course of action could take the form of the submission of the following ***three*** items:

1. Declaration by the sponsor that the regional (in the case of the European Union) or national regulatory authority is a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and has implemented the ICH E6 Guideline for Good Clinical Practice. In addition, a determination by the sponsor that an investigator's compliance with the ICH E6 Guideline for Good Clinical Practice will ensure that the investigator and sponsor comply with their respective obligations under 21 CFR part 312, other than the signature requirement on Form FDA 1572. (See the sponsor commitment example in the appendix.)

2. Commitment by the sponsor to collect from each investigator for whom the signature requirement was waived, a completed but unsigned Form FDA 1572 that includes all information in sections 1 through 8 of Form FDA 1572 and a signed statement containing commitments equivalent to the commitments specified in Section 9 of Form FDA 1572. (Note: In place of Form FDA 1572, the sponsor may choose to use an appropriate alternative template of its choice.) (See the sponsor commitment example in the appendix.)

3. Any templates or forms the sponsor intends to use to collect information and/or secure signed commitments from the applicable investigators. (See the investigator commitment example in the appendix.)

We encourage sponsors considering other approaches to discuss these with the appropriate review division.

42. *How and when should a sponsor submit the request to waive the signature requirement? [New 2021]*

The sponsor should submit the waiver request along with the necessary documentation supporting the waiver request in an amendment to the IND under which the study will be conducted.

The sponsor should submit the request to waive the signature on Form FDA 1572 when it determines that an investigator(s) cannot or will not sign Form FDA 1572.

If after a waiver request is granted, new investigators are added to this IND protocol who refuse or cannot sign the Form FDA 1572 and the sponsor wants to request a waiver of the Form FDA 1572 signature requirement, they will need to submit a new waiver request applicable to these new investigators (21 CFR 312.53(c)(1); 21 CFR 312.10)). When doing so, the sponsor should reference the protocol number, the date of the original request, and the date of any previous correspondence with FDA regarding the original waiver in a cover letter.

43. *Does the sponsor need to wait for the waiver request to be granted before initiating the study at that site?*
[New 2021]

Yes. The Agency will inform the sponsor in writing whether the Agency is granting each request to waive the 1572 signature requirement under 21 CFR 312.10(b), whether the request requires more information, or whether the request is denied. Only after either receiving a granted 1572 signature waiver or obtaining an appropriately signed Form FDA 1572 may a sponsor initiate the study at that site.

The sponsor should not assume that no response or a delayed response from the Agency means that the request for waiver has been granted.

If a waiver is granted, the sponsor should ensure that a copy of the waiver is maintained by the sponsor and the investigator so that it is available for review upon request.

44. *What does it mean to get a "1572 signature waiver"?*
[New 2021]

The waiver does not waive the sponsor's obligation to ensure that the investigator complies with the equivalent commitments expressed in the waiver request. Likewise, the waiver does not waive the sponsor's obligation to comply with all other applicable regulations.

Instead, after the Agency grants the waiver, the sponsor can conduct the study, under the IND, at sites at which investigators cannot or will not sign Form FDA 1572.

As explained in detail within this section, it is important that the sponsor establish an alternative course of action, acceptable to FDA, that will ensure that the investigator complies with commitments equivalent to those listed on Form FDA 1572.

45. *Is the waiver of the 1572 signature requirement a distinctly different waiver than an IRB requirement waiver?*
[New 2021]

Yes, they are distinct waivers. Waiving the 1572 signature requirement does *not* waive the IRB requirement, and a waiver of the IRB requirement under 21 CFR 56.105 does *not* waive the 1572

signature requirement. If a sponsor wishes to request a waiver of the IRB requirement, refer to question 12.[6]

If a request for waiver of the 1572 signature includes the use of an independent ethics committee (IEC) instead of an IRB, then the sponsor should obtain IRB waiver approval first or submit both waiver requests in one submission. FDA recommends that if a sponsor intends to request both a waiver of the 1572 signature requirement and a waiver of the IRB requirement, the sponsor does so in one submission. In this submission, the sponsor should:

1. Explicitly state, in the cover letter subject line, that it is requesting both waivers (waiver of the Form FDA 1572 signature and waiver of the IRB requirement); and

2. Ensure that both the request for waiver of the 1572 signature requirement and the request for waiver of the IRB requirement contain all information required to support each waiver request. The information supporting these requests should be separated and clearly marked.

46. ***Are there any special considerations regarding Form FDA 1572 signature waivers and pediatric studies?***
[New 2021]

Sponsors requesting waivers of the Form FDA 1572 signature requirement for IND studies that include pediatric subjects at foreign sites should take into consideration that any study that includes pediatric patients must demonstrate that the proposed study satisfies the requirements of 21 CFR part 50, subpart D. We recommend sponsors consult with FDA regarding any such request for a waiver under 21 CFR 312.10, as needed.

[6] See question 12 in the information sheet guidance for sponsors, clinical investigators, and IRBs *Frequently Asked Questions—Statement of Investigator (Form FDA 1572)*.

APPENDIX: EXAMPLES OF SPONSOR AND INVESTIGATOR COMMITMENTS
[New 2021]

SPONSOR COMMITMENT (EXAMPLE)

Sponsor XYZ declares that all the study sites under IND XXXX for which a waiver of the 1572 signature requirement is requested will be conducted in a country where the national regulatory authority is a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The country has implemented the ICH E6 Guideline for Good Clinical Practice (ICH E6) in regional and/or national legislation, norms, regulations, or competent authority administrative processes.

Sponsor XYZ will obtain a signed commitment to follow the recommendations in ICH E6 from each investigator at the study sites listed, using the form or template accepted by the FDA when granting the waiver request. Additionally, Sponsor XYZ will comply with the terms of the waiver. Further, Sponsor XYZ will ensure that each investigator at the study sites listed complies with the commitments contained in this waiver request.

Signature and date: _____

INVESTIGATOR COMMITMENTS (EXAMPLE)
[New 2021]

This study will be conducted consistent with the recommendations in ICH E6 Guideline for Good Clinical Practice[1] and all regional, national, or local regulations:

1. I agree to conduct the study or studies in accordance with the relevant, current protocol(s) and will only make changes in a protocol after receiving approval from the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

2. I agree to personally conduct or supervise the described investigation(s).

3. I agree to inform any participants or any persons who serve in the clinical trial that the drugs are being used for investigational purposes, and I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) or independent ethics committee (IEC) review and approval are met in accordance with national and regional legislation and the Declaration of Helsinki, and consistent with the recommendations in ICH E6.

4. I agree to report to the sponsor adverse events that occur in the course of the investigation(s) in accordance with national and regional legislation and the Declaration

[1] Refer to the most updated revisions of this guideline at https://www.ich.org/page/efficacy-guidelines.

of Helsinki, and consistent with the recommendations in ICH E6. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

5. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study or studies are informed about their obligations in meeting the investigator commitments in items 1 through 4 above.

6. I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with national and regional legislation and the Declaration of Helsinki, and consistent with the recommendations in ICH E6.

7. I will ensure that an IRB or an IEC that complies with the requirements of national and regional legislation and the Declaration of Helsinki, and that follows the recommendations in ICH E6, will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IEC all changes in research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

8. I agree to comply with all other requirements regarding obligations of clinical investigators and with all other pertinent requirements in accordance with national and regional legislation and the Declaration of Helsinki. I also agree to follow the recommendations in ICH E6.

Signature and date: _____