HREBA | Health Research Ethics Board of Alberta

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HREBA Policy on Signing FDA 1572

Article 1: Background and Purpose

This policy statement is intended to outline the REBs perspective on Investigator's signing US FDA Form 1572 and to set out alternatives that an investigator can propose to the sponsor so that neither the investigator nor the REB are obligated to comply with foreign (US) regulations.

The Statement of Investigator, Form FDA 1572 is an agreement (one-sided contract) signed by a clinical trial investigator to provide certain information to the clinical trial sponsor, and to assure the sponsor that he/she will comply with US FDA regulations related to the conduct of a clinical investigation of an investigative drug or biologic. The US FDA has created an Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs FAQs – Statement of Investigator (Form FDA 1572) which can be found at this link
https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm214282.pdf and details the rationale for the form and guides investigators concerning when it must be signed, and the information that it should contain.

It is a form used by Sponsors as evidence of the Investigator's attestation and commitment to conduct the study in accordance with the protocol, including (but not limited to) confirmation that the study will be conducted under the requirements of 21CFR Part 56 and as such, that the REB that reviews and approves the protocol at the site will similarly review the study in accordance with the US regulations. The HREBA committees operate in compliance with ICH GCP E6, Health Canada Food & Drugs Regulations, and the TCPS2. They are not governed by foreign country regulations unless they are obligated under a contractual agreement.

Article 2: Statement of Principle

HREBA strongly discourages researchers from signing US FDA Form 1572 and binding themselves and the REB that reviews the study to adhere to the requirements of the above-referenced US regulations. Canadian sites in US FDA regulated studies are considered foreign sites and Canadian investigators are considered to be foreign investigators. Canadian clinical trial sites are governed by Canadian clinical trial research regulations, including the Food & Drugs Act (Canada) which has expressly adopted the ICH-GCPs as the primary guidance document for the conduct of clinical trials in Canada, as well as by sponsor, institutional and research ethics board requirements.

As described below, the documents normally required for a Canadian clinical trial, including the signed protocol, the executed contract, the Qualified Investigator Undertaking and the Clinical Trial Site Information Form generally provide the kind of assurances and information that the US FDA requires.

Article 3: Requirements for Sponsors and Researchers

Under the US regulations, a US FDA Form 1572 (assurance by an investigator) is only required to be

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obtained from investigators for studies that are being conducted under an **IND (US Investigational New Drug Application)**. (Although a similar form is also required for US regulated investigational device studies.)

Under the US regulations, all **US** clinical trial sites **must** be subject to the US IND and all US clinical trial investigators must sign Form 1572.

All study sites (foreign or US) that are **listed** on the IND must comply with all applicable US regulations and the Principal Investigator (foreign or US) must sign Form 1572.

However, foreign sites (non-US) in a multi-center, multi-country clinical trial are not required to be listed on the IND. A US regulated multi-national study may include domestic (US) sites that are conducted under the IND and foreign (e.g. Canadian) sites that are not conducted under the IND.

Canadian sites can participate in a US IND study without signing a 1572 form. The data that is collected at their site can be used in support of the marketing application. (See below).

Article 3.1: Requirements for data from foreign sites in support of a marketing application

If a study is not conducted under the IND and the investigator does not sign a form 1572, the US regulations require that in order for the data to be able to be submitted to support a marketing application (new drug application NDA) the **only** requirement is that the study be conducted in compliance with 21 CFR 312.120

21 CFR 312 120 states that the data from a well-designed and well-conducted foreign clinical study not conducted under an IND will be acceptable as support for an NDA if:

- The study was conducted in accordance with good clinical practice (GCP) as set out in 21 CFR 312.120 and its sub-sections
- FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary

Details of what constitutes “in accordance with GCP” in are found in the March 2012 Guidance for Industry and FDA Staff found at this link:
https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf

The required elements include:

- Documentation of investigator qualifications
- A description of the research facilities
- A detailed summary of the protocol and study results
- Description of the drug substance and product
- Information showing that the effectiveness study is adequate and well controlled
- Name and address of the independent ethics committee (IEC) and confirmation that it was adequately constituted
- A summary of the IEC’s decision to approve the study
- A description of how informed consent was obtained
- A description of what incentives, if any were provided
- A description of how the sponsor monitored the study
- A description of how investigators were trained

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In general, all of these requirements are met, provided that the ICH-GCPs, Health Canada regulations, and TCPS2 requirements are followed.

However, if there is some situation where the US regulations are not being met in their entirety, sponsors may ask the US FDA to waive any of the required elements under 21CFR312.120 and provide a justification for the waiver request.

Article 3.2: Waiver of the requirements if Form 1572 is signed by the Investigator

In addition to allowing a sponsor to request a waiver under 21 CFR 312 120 (marketing application requirements), 21CFR56 105 allows a sponsor to apply for a waiver of some of the requirements in the US common rule legislation. Such a waiver will only be granted when alternative mechanisms for ensuring protection of the rights and welfare of human subjects are acceptable. The most common circumstance for such a waiver request is when an Independent Ethics Committee has overseen the study, and it has similar but not identical membership requirements when compared to a US IRB.

Article 4: Recommendations and Resources

Although HREBA committees (Cancer Committee and Clinical Trials Committee) can and do review US funded and US regulated studies in accordance with the US regulations, it is preferable if the requirements can be avoided or at least applied in as few studies as possible. HREBA recommends that the researchers ask clinical trial sponsors to exclude them from the US IND and that the researchers decline to sign the US FDA Form 1572.

The reasons for this recommendation are:

- Inclusion is unnecessary under US law
- Inclusion commits the site to compliance with foreign regulations that may not be fully understood or applied
- Inclusion provides an increased risk of non-compliance

If the Sponsor has already included the site in the IND, it is optional for researchers to ask that the sponsor or CRO request a waiver under 21CFR 56.105.

If a 1572 form is not signed, researchers must provide a statement to the sponsor that verifies that the US FDA can validate the data from the Canadian site through an on-site inspection. They can, if they desire, provide some form of an alternate assurance document, that confirms that the study will be conducted in accordance with domestic (Canadian laws), the ICH GCP E6, the protocol and the TCPS2.

A sample of such a form, adapted from a Nova Scotia Health Authority precedent and used with their permission follows:

“I, Dr. X, am a Principal Investigator for the clinical trial evaluating compound y, entitled (The study name) and bearing protocol number (as may be amended from time to time). This protocol is being conducted under my supervision at (name of institution) in (name of city and province).

In accordance with 21 CFR312.120 foreign studies and clinical sites need not be included under an IND and investigators from non-IND sites are not required to sign the FDA Form 1572.

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I have requested that the study sponsor not include my clinical site under the IND, which means that I am not required to sign Form 1572. I understand that data from my site may be submitted to the FDA to support clinical investigates and/or marketing approval(s) in the US. The FDA is welcome to validate the data from my site through an onsite inspection.

I am committed to conducting the study in accordance with Canadian research requirements and with internationally accepted ethical principles. I agree to conduct the study in accordance with the protocol, Good Clinical Practices as outlined in ICH GCPE6, Health Canada regulations pertaining to clinical trials and the Tri-Council Policy statement. Further, I will sign the Qualified Investigator Undertaking and provide necessary information for the Clinical Trial Site Information Form."

In support of this request, please refer to the following FDA Guidances:

- *https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm214282.pdf*
- *https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf*

If you have questions or require support for this position, please contact the HREBA office (info@hreba.ca).

(Adopted with permission from the University of British Columbia)

July 2025