U.S. FOOD & DRUG ADMINISTRATION

International Clinical Trials

ICH E6(R3) Updates

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Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

Objectives

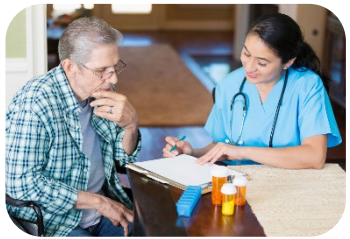
Highlight the significance of international clinical trials in FDA-regulated research

Discuss the ICH E6(R3) updates that are relevant to the responsibilities of clinical investigators

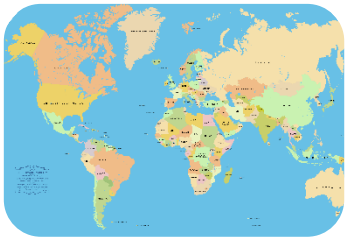
Importance International Clinical Trials

Access to diverse populations

Enhanced generalizability of results



Accelerated patient recruitment



Addressing health issues that affect multiple regions

Enables sponsors to enter multiple markets simultaneously

Clinical Trial Data for Drug Approvals

***80%**

approved NDAs and BLAs contained data from global sources.

fda.gov/cdersbia

*http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf

Clinical Trials Conduct

- Clinical trails are increasingly global
- They are conducted under a variety of scenarios
- Some trials are based solely on foreign clinical data
- The inclusion of U.S. participants is crucial for FDA evaluation especially if the trial results are intended to support regulatory approval in the United States.

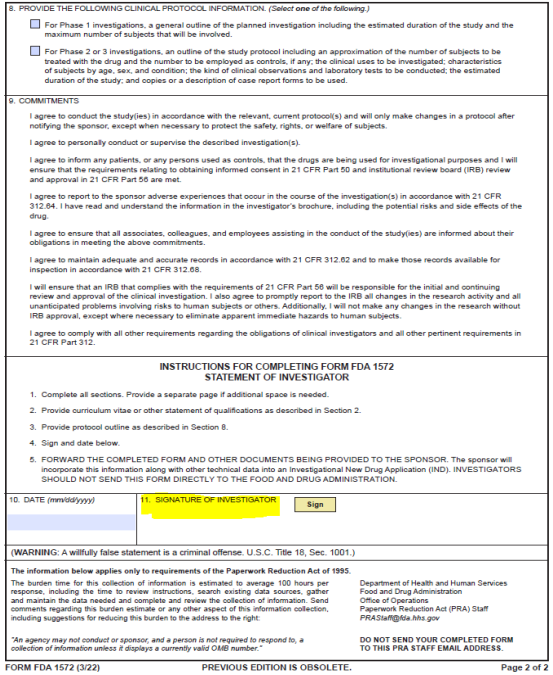
Trials Outside United States

- IND is not required for clinical trials outside the United States
- If a clinical trial is conducted under an IND, IND requirements must be met unless waived

An IND is a request for FDA authorization to ship an investigational drug across state lines for use in human clinical trials.
The investigator responsibilities are covered under Part 312.60 to 312.70 Investigational New Drug Application Regulations

Form FDA 1572

Required for clinical investigations conducted under an IND.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2025
See OMB Statement on Reverse.

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)).

1. NAME AND ADDRESS OF INVESTIGATOR

Name of Clinical Investigator

Address 1 | Address 2

City | State/Province/Region | Country | ZIP or Postal Code

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED *(Select one of the following.)*

☐ Curriculum Vitae ☐ Other Statement of Qualifications

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED — CONTINUATION PAGE for Item 3

Name of Medical School, Hospital, or Other Research Facility

Address 2 | Country | ZIP or Postal Code

FACILITIES TO BE USED IN THE STUDY — CONTINUATION PAGE for Item 4

Address 2 | Country | ZIP or Postal Code

BOARD (IRB) THAT IS RESPONSIBLE FOR — CONTINUATION PAGE for Item 5

Address 2 | Country | ZIP or Postal Code

"None")

CONTINUATION PAGE – for Item 6

(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR

OUS EDITION IS OBSOLETE. Page 1 of 2

8. PROVIDE THE FOLLOWING CLINICAL PROTOCOL INFORMATION. *(Select one of the following.)*

☐ 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. Provide a separate page if additional space is needed.
2. Provide curriculum vitae or other statement of qualifications as described in Section 2.
3. Provide protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND OTHER DOCUMENTS BEING PROVIDED TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. DATE *(mm/dd/yyyy)* | 11. SIGNATURE OF INVESTIGATOR — Sign

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

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

The burden time for this collection of information is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"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 number."

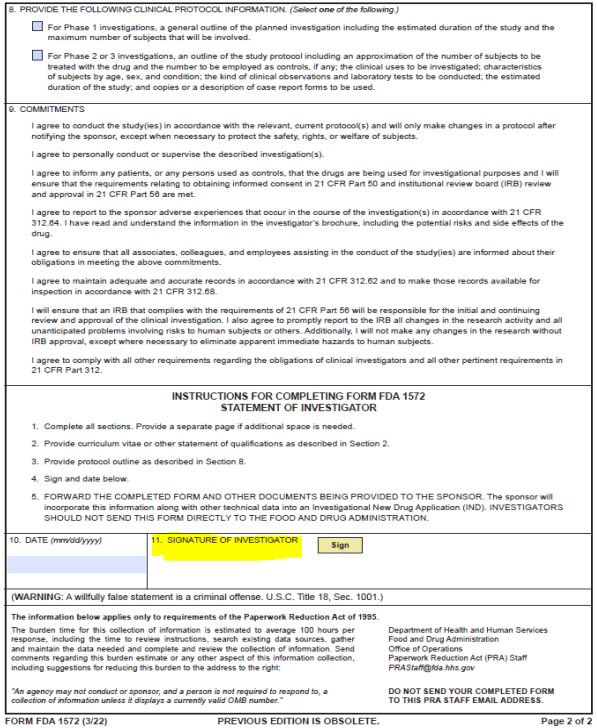
DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF EMAIL ADDRESS.

FORM FDA 1572 (3/22) PREVIOUS EDITION IS OBSOLETE. Page 2 of 2

Form FDA 1572 is Statement of Investigator required for clinical investigations under an IND.

Form FDA 1572 Signature Waiver

- Clinical investigators conducting FDA regulated study outside the US may request waiver from FDA 1572 Signature.
- The waiver allows a study to proceed without a signed Form FDA 1572.
- Waiver requires alternative commitments such as following ICH E6 Good Clinical Practice, ensuring informed consent and IRB/IEC approvals



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FDA Expectations of Clinical Investigators During Inspection

Adherence to Code of Federal Regulations

Knowledge about the clinical trial investigation

Understanding of their regulatory responsibilities

Inspection Areas of Focus

1) Protocol – adherence

2) Review of IC and IRB oversights

3) Comparison of line listings with source documents and verification of reported data and quality

4) Review of enrollment process Review of monitoring activities

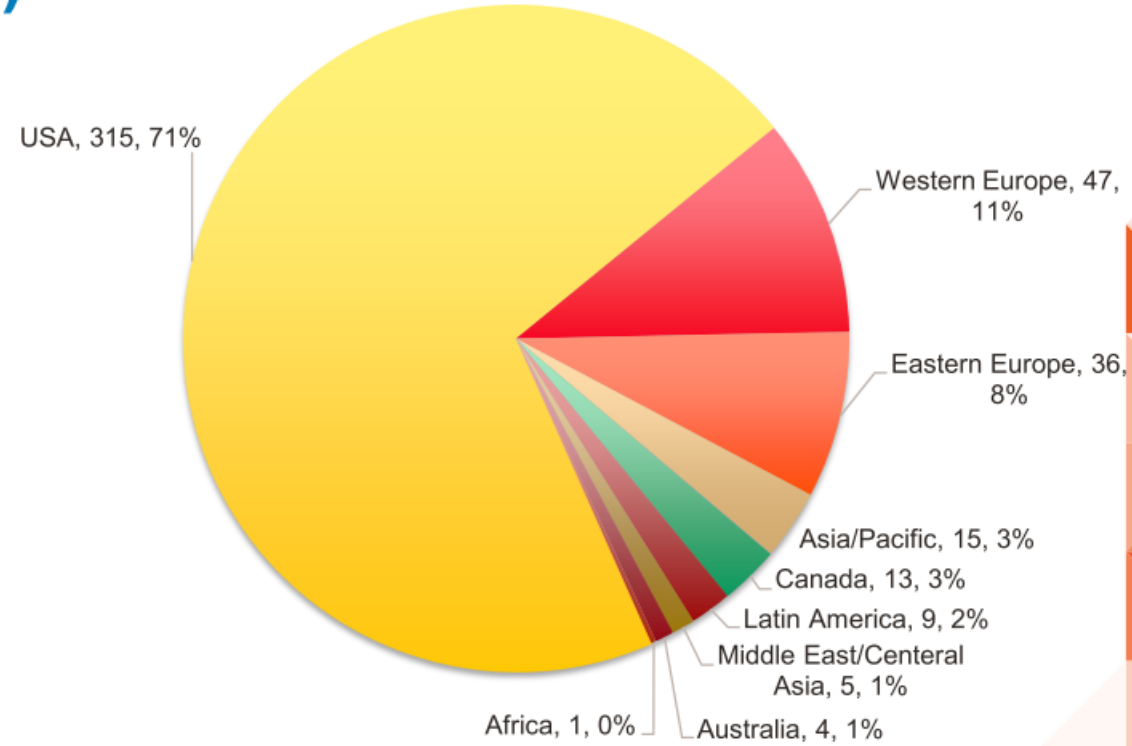
5) Review of reporting to sponsor

6) Review of compliance with applicable regulations (e.g., Safety report, financial disclosure and updates)

7) Review of test article control; review of records custody and retention

Clinical Investigator Inspections-Location (CDER, FY2023)

- A total of 445 clinical investigator inspections.
- ~70% of clinical investigator inspections are associated with NDA/BLA occur in the US.
- ~30% of clinical investigator inspections are associated with NDA/BLA occur outside the USA



Common Inspectional Observations

- Failure to follow investigational plan/protocol
- Inadequate/inaccurate records
- Inadequate drug accountability
- Failure to obtain and/or adequately document informed consent
- Failure to report adverse drug reactions and issues related to IRB communication

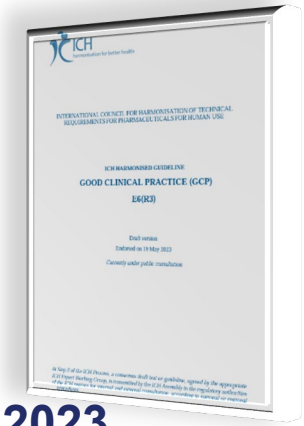
Acceptance of Foreign Data and ICH E6 Updates

Acceptance of Foreign Data

The FDA accepts data from foreign studies not conducted under an IND, provided the

- study is well-designed and properly conducted.
- study is carried out by qualified investigators.
- FDA can validate the data through inspections if needed.
- study is conducted in compliance with **GCP**

ICH E6 Revisions



E6: Approved

E6(R2): Approved

10 June 1996

19 May 2023

1 May 1996

9 Nov. 2016

E6(R1): Post-Step 4 editorial corrections

E6(R3): Draft guideline available for public consultation

Purposes of the ICH E6 Updates

- To update and modernize Good Clinical Practice guideline.
- To provide guidance applicable to various clinical trial designs and promote innovation.
- To enhance the focus on a proportionate, risk-based approach to the design and conduct of clinical trials.
- To address the complexities of clinical trials within the current global regulatory environment.

Development Strategy for E6(R3)

Annex 1

- Considerations for interventional clinical trials

Annex 2

- Additional considerations

When complete, E6(R3) will be composed of an overarching principles and, Annex 1 and Annex 2.

Draft Published | **In the Making**

Key Updates in ICH E6 (R3) Relevant to Clinical Investigators

Recommends to use **varied approaches** to IC

Clarifies overall **training requirements** for trial staff by saying training should correspond to what is necessary

Clarifies expectations regarding **the use of computerized systems** provided by the sponsor vs those available at clinical practice

Clarifies the expectations for the sponsor and investigator regarding **use of service providers**

Clarifies expectations regarding **identification and maintenance** of source records and timely data review

Clarifies requirements for **delegation documentation**, e.g., where the clinical trial activities are performed in accordance with routine clinical care, delegation may not be needed.

What is Next and Timeline?

Annex-1 draft has been published

Annex 2 is being developed

When finalized, the guidelines are expected to establish harmonized GCP standards

Training program is being developed that clarifies or provides supplementary explanation

The final E6(R3) will replace the current E6(R2) guideline that has been in effect since November 2016

Challenge Question #1

Which of the following statement is true regarding clinical investigations conducted outside the United States?

A. Investigators must always submit an IND to the FDA

B. All clinical trials must adhere to FDA regulations regardless of location

C. IND submissions are only required for Phase III trials

D. Investigators are not required to conduct their investigations under an IND

Challenge Question #2

Why is it important for the FDA to validate the data from clinical trials submitted in marketing applications?

A. To determine whether the clinical trial participants were compensated appropriately

B. To determine the commercial value of the product and ensure it will be profitable

C. To guarantee that the clinical trial investigators receive appropriate compensation for their work

D. None of the above

Take Home Points

- International clinical trials are vital for generating data to support drug approvals,

- Clinical investigators should fully understand FDA regulatory requirements and ICH E6 Good Clinical Practice standards to ensure successful trial conduct and data acceptance by the FDA.

Resources

1. Sec. 314.106 Foreign Data
2. FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions | FDA
3. FDA Inspections of Clinical Investigators
4. Clinical Trials Guidance Documents
5. ICH E6(R3) Guidelines – Good Clinical Practice
6. Form FDA 1572: Investigator Responsibilities
7. The Future of International Clinical Trials
8. Trends in Global Clinical Trials

U.S. FOOD & DRUG ADMINISTRATION

Thank You!

Kassa.Ayalew@fda.hhs.gov