Integrating Quality into Clinical Trials

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Office of the Commissioner | US FDA

FDA Clinical Investigator Training Course – December 6-7, 2023

Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration

Learning Objectives

- Understand the regulatory perspective on clinical trial quality
- Identify the federal regulations covering clinical research and clinical investigator obligations
- Discuss methods that can be used to support compliance with federal regulations and study protocol requirements

Clinical Trial Quality

- Quality as **fitness for purpose**.
- The **purpose** of a clinical trial
  - to generate reliable information to answer the research questions and support decision-making
  - while protecting study participants.
- **The quality of the information** generated should therefore be sufficient **to support good decision-making.**

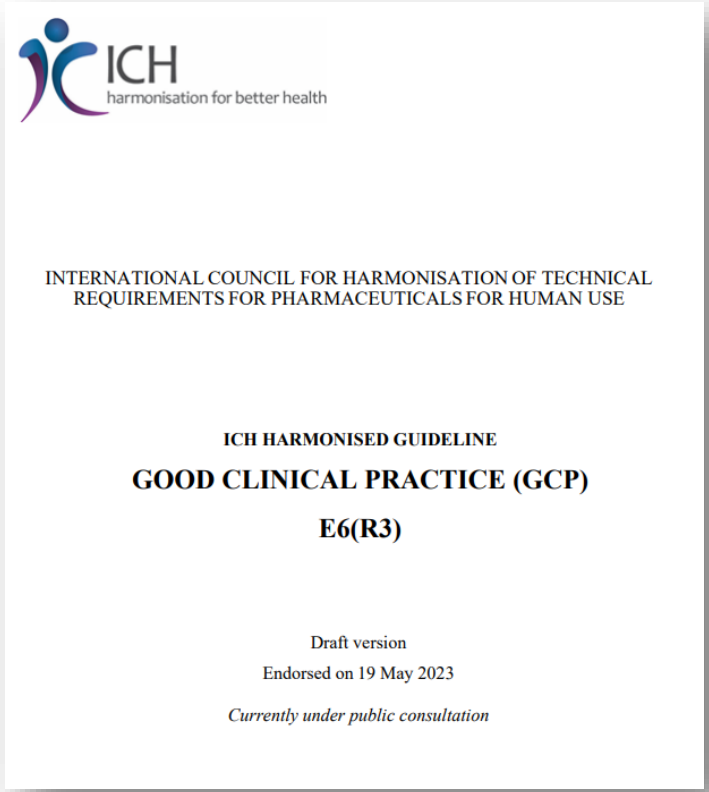
Source: ICH E8 (R1), General Principles for Clinical Trials

Modernizing The Conduct of Clinical Trials

Harmonizing Good Clinical Practice Guidelines - ICH E6(R3) – GCP

ICH E6 is unique as the only harmonized guideline among the global regulatory community for clinical trial conduct

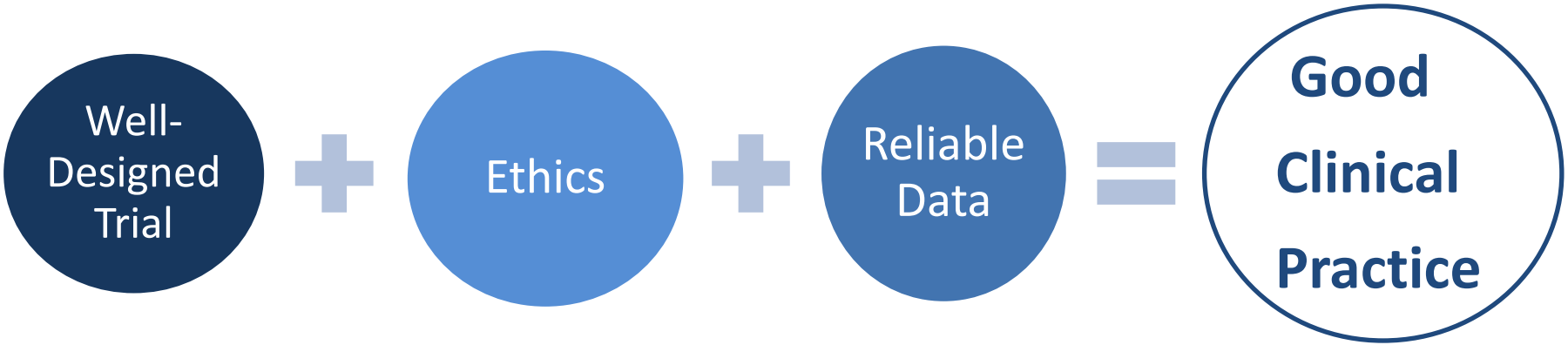
- The draft E6(3) guideline sets a foundation for **practical/feasible** expectations for GCP to facilitate clinical trials across settings
- Encourages **fit-for-purpose** approaches
- **Minimize burden** and focusing resources on what matters most to make clinical trials more efficient globally



https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

Good Clinical Practice, Simplified

FDA oversees clinical trials to ensure they are designed, conducted, analyzed and reported according to federal law and good clinical practice (GCP) regulations.



Trial Quality

Multiple parties have responsibility for trial quality and participant protection, including:

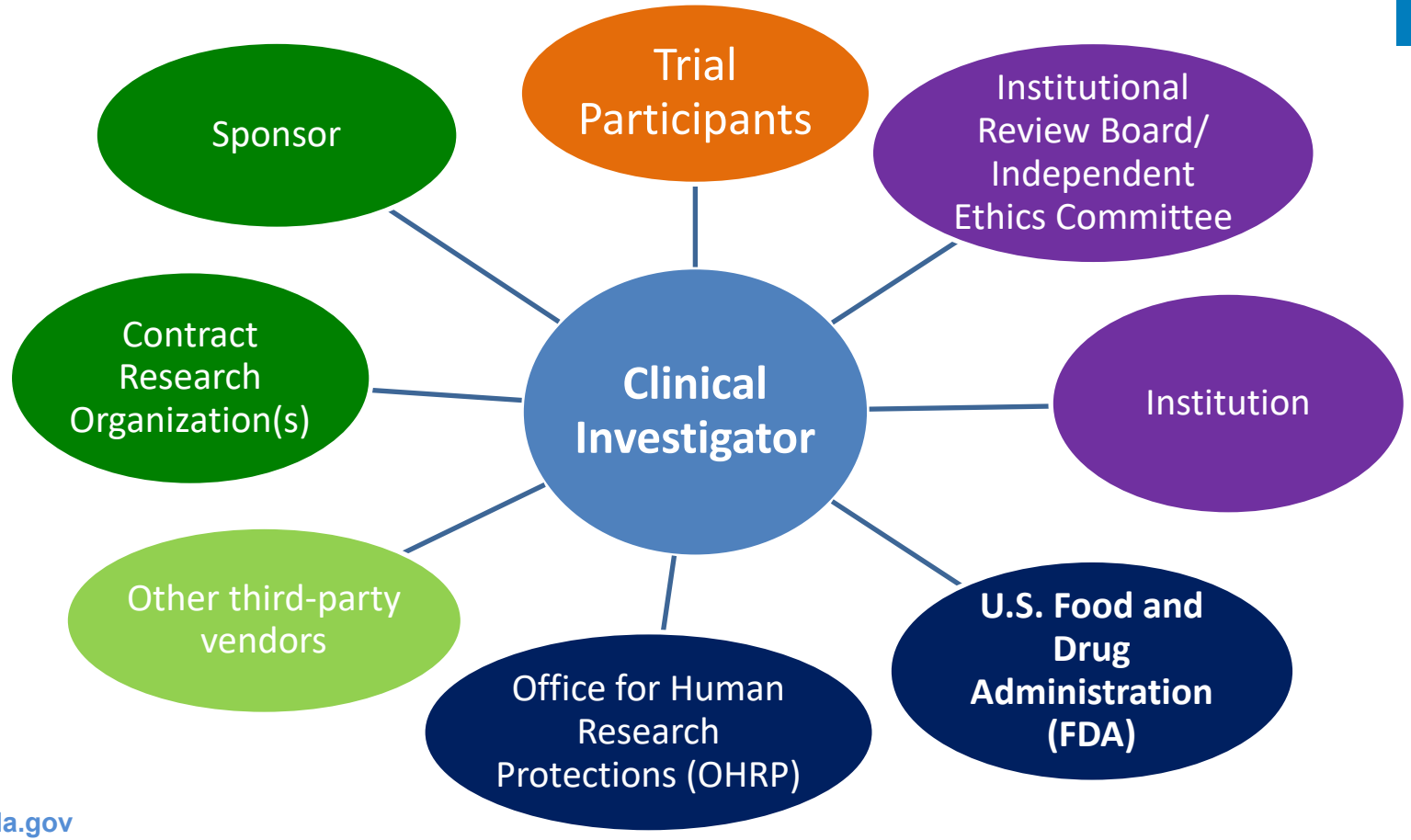
- Sponsors
- Contract Research Organizations (CROs)
- Institutional Review Boards
- **Clinical Investigators**

Who is an Investigator?

- An individual **who actually conducts a clinical investigation** (i.e., under whose immediate direction the drug is dispensed to a subject.)
- In the event an investigation is conducted by a team of individuals, the investigator is **the responsible leader** of the team.

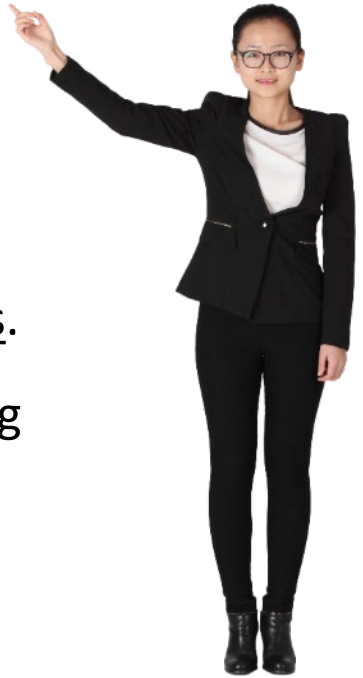
21 CFR 312.3

Clinical Trial Environment



Question

Can there be co-investigators?



- ***ANSWER:*** **Yes and No.**
- Yes, for your needs but No for regulatory purposes.
- Each co-investigator is fully responsible for fulfilling all obligations of an investigator; each must sign a separate Form FDA- 1572.

Question

Does the investigator have to be a medical doctor?

ANSWER: No.

A physician can be a sub-investigator to perform those study functions requiring the appropriate level of medical expertise.
[21 CFR 312.53].

Who is a “Sponsor-Investigator”?

- An individual who **both initiates and conducts an investigation**, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual
- The requirements applicable to a sponsor-investigator include both those applicable to an investigator and those applicable to a sponsor.

[21 CFR 312.3]

Sponsor-Investigators: Know the ClinicalTrials.gov Requirements

42 CFR Part 11

- Clarifies and expands requirements for the submission of clinical trial registration and results information
- Issued September 21, 2016
- Effective Date: January 18, 2017
- Compliance Date: April 18, 2017

FDA ClinicalTrials.gov Webinars

DATE

On Demand

Visit CDER Small Business and Industry Assistance Page

ABOUT THIS EVENT

In a three-part webinar series, FDA provides a general overview of ClinicalTrials.gov and relevant definitions, laws, and regulations for complying with ClinicalTrials.gov registration and results information submission requirements. Participants will gain an understanding of CDER's role and responsibilities with respect to ClinicalTrials.gov oversight and will hear examples of compliance and enforcement activities CDER has taken to encourage compliance.

FDA Requirements for Clinical Research and Clinical Investigators

Legal Framework

Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 505(i) is the statutory authority for FDA's oversight of clinical investigations to test safety and effectiveness

Code of Federal Regulations (CFR)

Regulations promulgated under Section 505(i) describing FDA's authority over the conduct of clinical investigations

Guidances

Advisory only, to assist regulated entities in complying with the regulations

FDA Expectations of Clinical Trial Investigators

Adherence to the Code of Federal Regulations (CFR)

- Knowledge of Clinical Investigator regulations
- Understanding of Clinical Investigator responsibilities

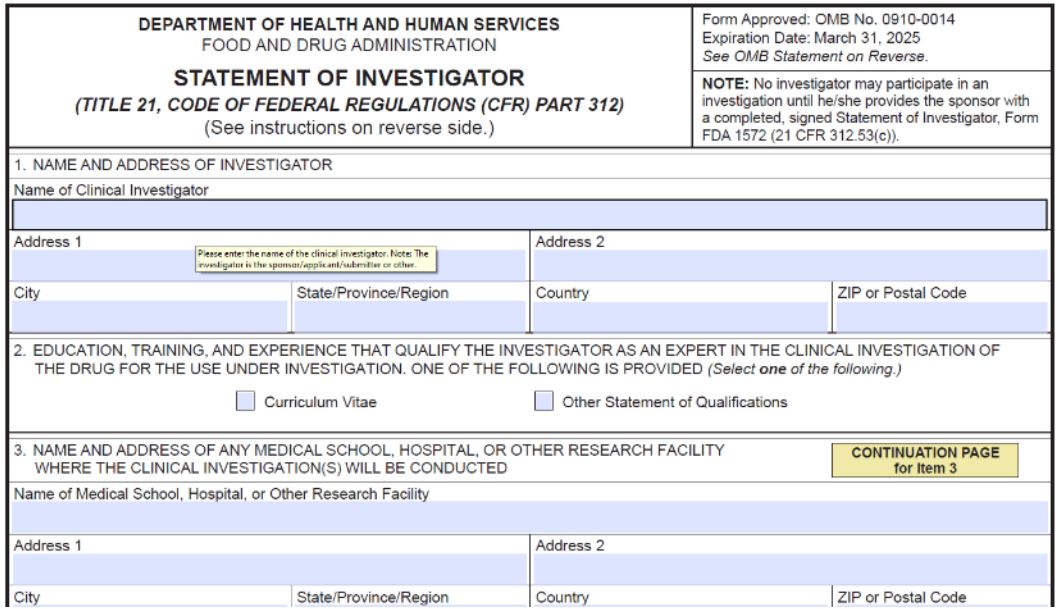
FDA Regulations Relating to Good Clinical Practice and Clinical Trials

These regulations are intended to ensure the integrity of clinical data on which product approvals are based and to help protect the rights, safety, and welfare of human subjects.

- 21 CFR 11 – Electronic Records & Signatures
- 21 CFR 50 – Informed Consent
- 21 CFR 54 – Financial Disclosure
- 21 CFR 56 – Institutional Review Boards
- 21 CFR 312 – Investigational New Drug Applications
- 21 CFR 314 – New Drug Applications
- 21 CFR 320 – Bioavailability & Bioequivalence
- 21 CFR 601 – Biologic License Applications
- 21 CFR 812 – Investigational Device Exemptions
- 21 CFR 814 – Premarket Approval of Medical Devices

Statement of Investigator, Form FDA 1572

- 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)]



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

Please enter the name of the clinical investigator. Note: The investigator is the sponsor/applicant/submitter or other.

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

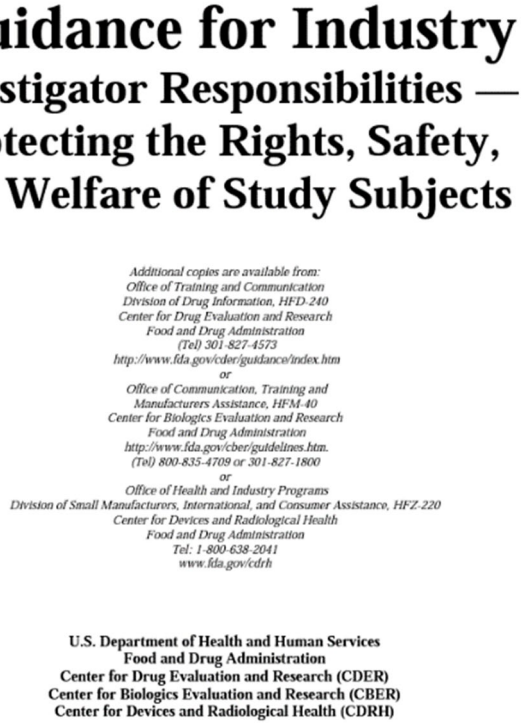
CONTINUATION PAGE for Item 3

Name of Medical School, Hospital, or Other Research Facility

Address 1 | Address 2

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

Investigator Responsibilities: Oversight



Guidance for Industry

Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication, Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
http://www.fda.gov/cber/guidelines.htm.
(Tel) 800-835-4709 or 301-827-1800
or
Office of Health and Industry Programs
Division of Small Manufacturers, International, and Consumer Assistance, HFZ-220
Center for Devices and Radiological Health
Food and Drug Administration
Tel: 1-800-638-2041
www.fda.gov/cdrh

U.S. Department of Health and Human Services
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)

Clarifies FDA's expectations concerning the investigator's responsibility

(1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties and

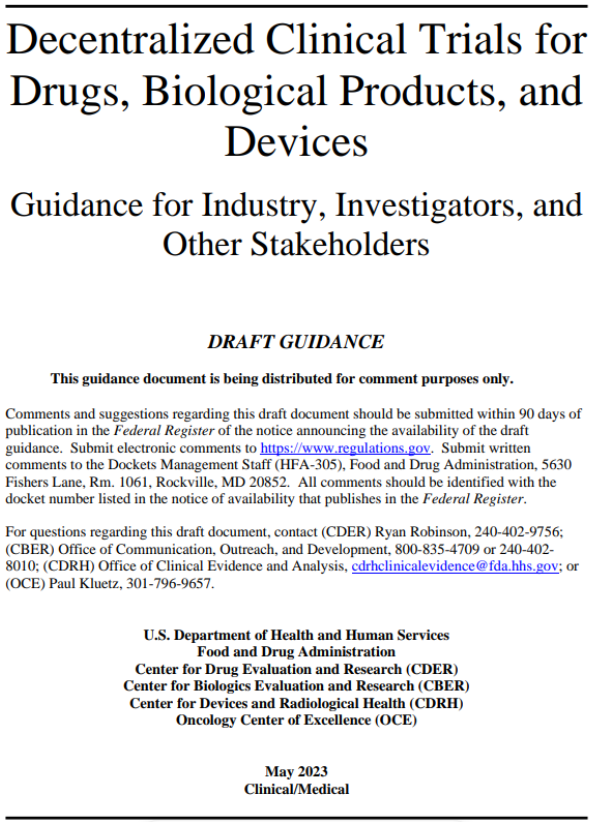
(2) to protect the rights, safety, and welfare of study subjects.

Decentralized Clinical Trials Draft Guidance

DCTs have the potential to expand access to more diverse patient populations and improve trial efficiencies.

DCTs may enhance convenience, reduce the burden on caregivers, and facilitate research on diseases affecting populations with limited mobility or access to traditional trial sites.

Remote participation may help improve trial participant engagement, recruitment, enrollment, and retention of a meaningfully diverse clinical population.



Decentralized Clinical Trials for Drugs, Biological Products, and Devices

Guidance for Industry, Investigators, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ryan Robinson, 240-402-9756; (CBER) Office of Communication, Outreach, and Development, 800-835-4709 or 240-402-8010; (CDRH) Office of Clinical Evidence and Analysis, cdrhclinicalevidence@fda.hhs.gov; or (OCE) Paul Kluetz, 301-796-9657.

U.S. Department of Health and Human Services
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)
Oncology Center of Excellence (OCE)

May 2023
Clinical/Medical

Adapted from L. Sacks

Investigator's Role and Responsibilities

- Responsible for the conduct of the DCT and the oversight of individuals delegated to perform trial-related activities
- A key difference for DCTs is the extent to which the investigator uses telehealth, trial personnel working remotely, local healthcare providers (HCP), and/or Digital Health Technology (DHT) in the conduct of the trial
- Decentralized features may necessitate additional training, coordination, and standard operating procedures to ensure consistent implementation

Documentation: Investigators, Subinvestigators, Local HCPs

- Drug trials (Form 1572)
  - When trial personnel contribute directly and significantly to the trial data, they should be included on Form FDA 1572 as subinvestigators
  - Local HCPs (as defined in the draft guidance) should not be listed on Form FDA 1572 as subinvestigators.
  - However, local HCPs should be included in a task log.
- For device trials, local HCPs are generally not considered investigators and should not be included in the IDE list of investigators. However, these local HCPs should be included in a task log

Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs *Frequently Asked Questions – Statement of Investigator (Form FDA 1572)* (May 2010)

Challenge Question #1

Per the draft DCT guidance, local health care providers should be listed in the:

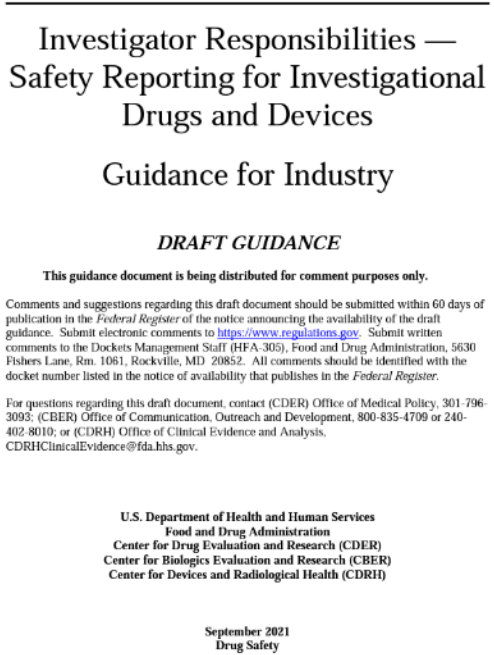
A. Form FDA 1572 as a sub-investigator

B. 1572 and the delegation log

C. Task log

D. 1572 and task log

IND Safety Reporting: Investigator Key Responsibilities



Investigator Responsibilities — Safety Reporting for Investigational Drugs and Devices

Guidance for Industry

DRAFT GUIDANCE

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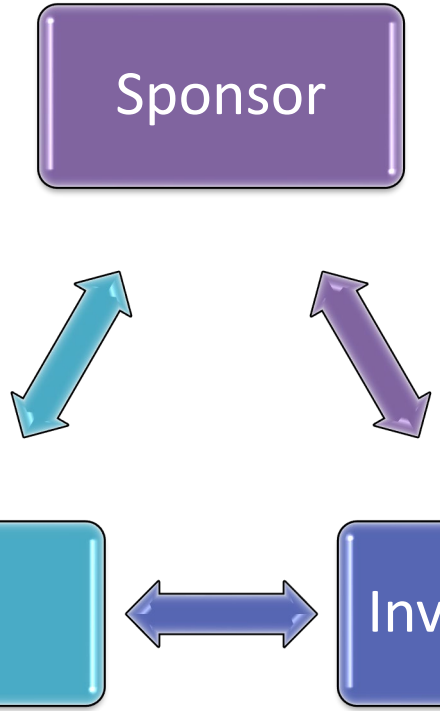
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

September 2021
Drug Safety

- Determine if adverse event (AE) is serious
- Report SAEs to the sponsor immediately (21 CFR 312.64)
- Record non-serious adverse events and report them to the sponsor as specified in the protocol
- Review IND safety reports and report any changes in activity and all unanticipated problems involving risk to human subjects or others to the IRB (21 CFR 312.66)
- FDA generally considers a serious and unexpected adverse event that meets the criteria for an IND safety report to be an unanticipated problem involving risk to human subjects or others that therefore must be reported to the IRB by the investigator

Continuous Process Safety Reporting

- Evaluates SAEs and submits IND safety reports
- Evaluate aggregate safety signals
- Modifies IB, Protocol, ICF where necessary



- Determine if AE is serious and report SAEs to sponsor
- Review IND safety reports
- Modify ICF, where necessary

- Follow written procedures
- Review and approve amended protocol and/or ICF
- Review research and unanticipated problems

- Report unanticipated problems to the IRB
- Obtain IRB approval of any amended IC and protocol amendment

Challenge Question #2

Who has responsibility for reporting unanticipated problem involving risk to human subjects or others to the IRB :

A. Sponsor

B. Investigator

C. Contract Research Organization

D. All of the above

Informed Consent Requirements

- 21 CFR 312.60: Investigator must obtain the informed consent of each human subject to whom the drug is administered, except as provided in §§ 50.23 or 50.24 of this chapter.
- Required content as per 21 CFR part 50.25
- Opportunity for study participants to ask questions and receive answers to those questions as per 21 CFR 50.20

What is Informed Consent?

- **Not** just a signature or a document

- An **ongoing <u>process</u>** that must occur before any study-related procedures/tests are conducted

QUESTION

Does the investigator have to sign the informed consent?

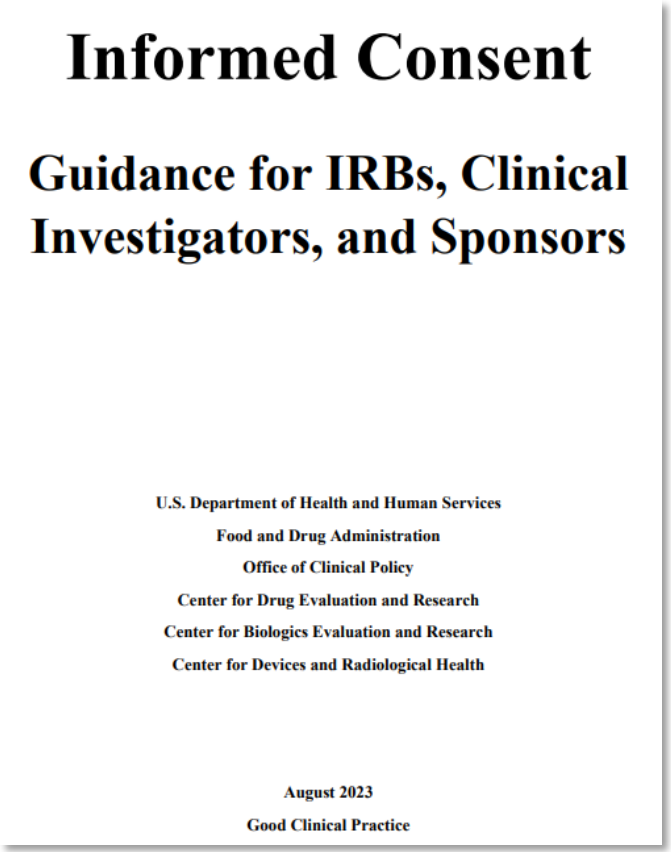
ANSWER: **NO**

Signing/dating by person conducting the informed consent discussion is part of ICH E6, but not FDA regulations

2023 Informed Consent Guidance

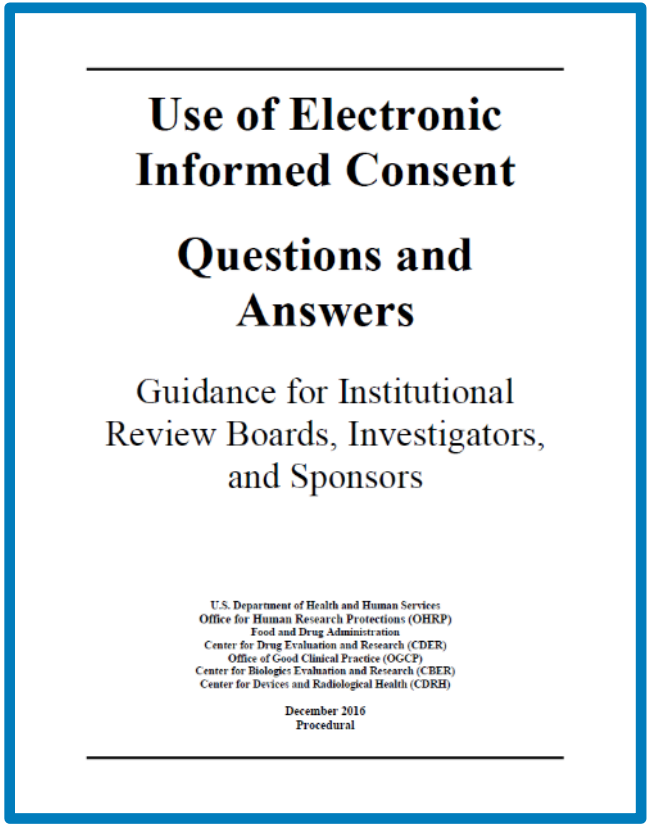
- Final Guidance structure
  - General guidance on FDA's regulatory requirements for informed consent
  - Discussion of the roles of IRBs, clinical investigators, sponsors, and FDA related to informed consent,
  - Frequently asked questions

https://www.fda.gov/media/88915/download



Electronic Informed Consent

- Final Guidance published in December 2016
- Provides recommendations on the use of various electronic media (e.g., text, graphics, audio, video, podcasts and interactive Web sites) to obtain and document informed consent



Use of Electronic Informed Consent

Questions and Answers

Guidance for Institutional Review Boards, Investigators, and Sponsors

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

December 2016
Procedural

Proactive Practices

Pro-active Practices for Protocol Compliance

1. Assess how the protocol will translate to operations at your site:

Participant flow through study visits

Activities needed to carry out that protocol

Data required to be collected

Access to specialized expertise or equipment

Study specific nuances (e.g., AE of special interest)

2. Do beta-testing/dry-runs – who will do what, how/where documented, et al

3. Do real-time review of visit records/data to identify and address issues early

ICH E8(R1)
General Considerations for Clinical Trials

Provides an:

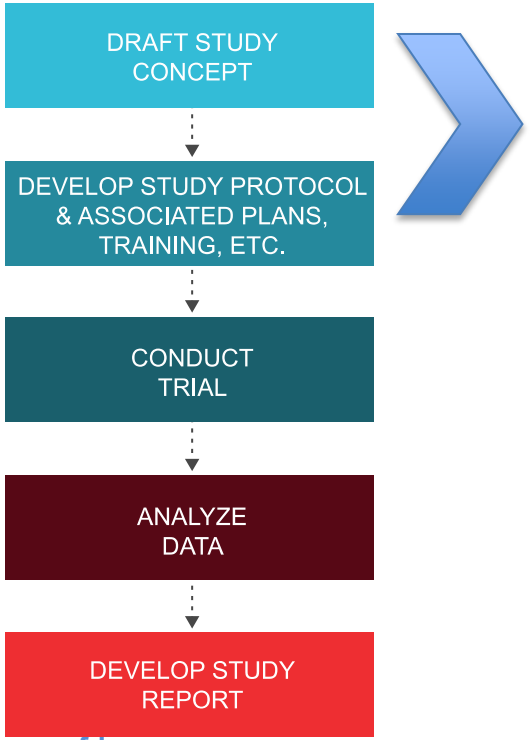
- Overall guide to all the ICH Efficacy Guidelines
- Overview of types of clinical studies conducted during product lifecycle
- **Quality considerations in the design and conduct of clinical studies – Quality by Design (QbD)**

Highlighting the Importance of Clinical Trials in ICH E6 (R3)

Clinical trials are a **fundamental part of clinical research** that support the development of new medicines or uses of existing medicines. Well designed and conducted clinical trials help answer key questions in health care and drug development. Their results are **essential for evidence-based healthcare decisions**.

Trials with inadequate design and/or poorly conducted trials may **place participants safety at risk and yield inadequate or unreliable evidence**. **They waste resources** and the efforts and time of investigators and participants and may **not align with ethical principles**.

Protocol Development: A Crucial Component of Quality by Design



1. Identify critical aspects of trial design
2. Tailor design to avoid errors that matter
3. Streamline trial where feasible
4. Verify proposed design is consistent with important scientific question to be addressed
5. Highlight important risks not eliminated through study design that may be better addressed in operational plans

https://ctti-clinicaltrials.org/our-work/quality/quality-by-design/

Case Example

Marketing Submission

- Contained large randomized, blinded, placebo-controlled cardiovascular outcomes study
- Independent adjudication committee for primary endpoint (MACE - Major Adverse Cardiovascular Events)
- Study powered based on predicted number of primary endpoint events

Case Example

Site “A”

- During FDA review, site flagged for inspection based on:
  - Enrollment (approximately 5% subjects in study)
  - Data trends suggesting under reporting of events (primary efficacy and safety)
- Inspection:
  - On record review, multiple examples identified that appeared consistent with MACE event, but adjudicated negatively by independent adjudication committee
  - Per CI, when event occurred outside of the site’s network, it was almost impossible for site staff to obtain requested records needed by adjudication committee due to litigious climate of community

Case Example

Impact of “Site A” type findings:

- Predicted number of primary endpoint events not reached in enrolled population (study underpowered)
- Sponsor needed to re-estimate sample size substantially increasing enrollment
  - Gain regulatory authority agreement
  - Implement protocol amendment
  - Increased cost
  - Increased trial length

Case Example

Hindsight is 20 – 20, but might the issues encountered have been prevented had a well informed QbD process been used during the design and planning of this study?

Summary

- Clinical investigators play a critical role in ensuring trial quality
- Sponsor-investigators have additional responsibilities, including for transparent reporting of results of applicable clinical trials.
- Both must ensure that all staff have a clear understanding of the protocol and their responsibilities under FDA regulations
- At stake is public confidence and participation in clinical trials- and ultimately the availability of safe and effective products

U.S. FOOD & DRUG ADMINISTRATION

Questions?

Ann Meeker-O'Connell
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Office of Clinical Policy and Programs
Office of the Commissioner | US FDA

gcpquestions@fda.hhs.gov

Resources

- FDA Regulations (and Preambles) for Good Clinical Practice (GCP) and Clinical Trials
- Clinical-trial related guidance documents (searchable)
- Clinical Trials and Human Subject Protection
- CDER's Good Clinical Practice website