

Regulations and Good Clinical Practice Guidance

At the conclusion of this chapter, investigators will be able to answer the following core questions:

- With what regulations should an investigator be familiar?
- What is GCP?
- What is HIPAA?
- What is ICH?
- What is ISO?

In order to conduct high-quality, compliant clinical trials, investigators must have a thorough understanding of the regulations and relevant guidance, as well as of the drug development process. The regulations with which investigators should be familiar, depending on the areas in which they work, are:

- 21 CFR Part 11—Electronic Records; Electronic Signatures
- 21 CFR Part 50—Protection of Human Subjects
- 21 CFR Part 54—Financial Disclosure by Clinical Investigators
- 21 CFR Part 56—Institutional Review Boards
- 21 CFR Part 312—Investigational New Drug Application
- 21 CFR Part 314—New Drug Applications
- 21 CFR Part 600—Biological Products: General
- 21 CFR Part 601—Applications for FDA Approval of a Biologic License
- 21 CFR Part 812—Investigational Device Exemptions
- 21 CFR Part 814—Premarket Approval of Medical Devices

- 45 CFR Part 46—Protection of Human Subjects
- 45 CFR Parts 160 and 164—HIPAA Privacy Rule

Parts 11, 50, 54, 56, and 312/812 (drugs-biologics/medical devices) encompass the Good Clinical Practice (GCP) sections of the Code of Federal Regulations, and they are the regulations pertinent to conducting clinical trials in the U.S. Parts 600 and 601 pertain to biologics marketing, parts 314 and 814 pertain to drug/device marketing, and 45 CFR Part 46 pertains to studies conducted with government funding. 45 CFR Parts 160 and 164 comprise the HIPAA Privacy Rule.

The regulations tell us what actually is required by the FDA and/or the HHS for conducting clinical studies overseen by these bodies. They cover the responsibilities of research sponsors, clinical investigators and IRBs for conducting trials involving human subjects.

FDA Guidance and Information Sheets

The FDA publishes a number of guidance documents (including information sheets) that are very useful in the conduct of clinical trials. These guidance documents offer more detailed explanations of the regulations, including the current interpretations and thinking of the FDA. They often include frequently asked questions and answers for items of particular interest. Although the guidance documents do not carry the weight of regulations, it is highly recommended they be understood, as they are the FDA's expectations for the conduct of trials. Links to specific guidance documents can be found on the FDA web site. Some of the more useful guidance documents include:

- FDA Information Sheets for IRBs and Investigators—1998 Update¹
- Good Clinical Practice in FDA Regulated Clinical Trials²
- Guidance: General Considerations for Clinical Trials³
- Exception from Informed Consent Requirements for Emergency Research⁴
- Recruiting Study Subjects⁵
- Disqualified/Restricted/Assurance List for Clinical Investigators⁶

FDA Compliance Program Guidance Manuals

There also are FDA Compliance Program Guidance Manuals (CPGMs or compliance programs) that may be helpful to an investigator. These are the instruction manuals that FDA personnel use when they conduct inspections

of clinical investigators, sponsors and IRBs. They include:

- CPGM 7348.811 for Clinical Investigators⁷
- CPGM 7348.810 for Sponsors, Monitors and Contract Research Organizations⁸
- CPGM 7348.809 for IRBs⁹

Of particular interest is the compliance program for clinical investigators (7348.811), which describes in detail what the FDA evaluates during its inspections of clinical investigators.

NIH-Regulated Research

Clinical trials conducted under the auspices of HHS, such as an NIH-sponsored or NIH-funded trials, are governed by HHS regulations, which differ somewhat from FDA regulations. For example, HHS regulations contain specific sections on working with vulnerable subjects, such as pregnant women and prisoners, that are not found in the FDA regulations. HHS regulations for clinical trials are described in 45 CFR 46. An Appendix in this book provides a detailed comparison of the FDA and HHS Human Subject Protection Regulations.

FDA Bioresearch Monitoring Program

FDA's Bioresearch Monitoring (BIMO) Program requires that FDA-regulated biomedical research conducted by investigators conforms to GCP standards as found in the FDA regulations. To ensure GCP standards are followed, the FDA inspects clinical trials. Note that what the FDA calls inspections are commonly called audits by others. The FDA's program of inspections of clinical trials is called the BIMO program, and covers all of the parties involved in regulated clinical trials, including clinical investigators, IRBs, sponsors, monitors and CROs. Additional BIMO inspection programs also cover non-clinical and bioequivalence studies.

Good Clinical Practice (GCP)

GCP is the accepted set of procedures for conducting clinical trials. In addition to FDA regulations, investigators conducting drug and biological product clinical trials also should be familiar with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use—also known as the ICH Guideline for Good