Clinical trials in the U.S. and abroad are governed by a wide variety of regulations, guidelines and standards. This excerpt from CenterWatch's *The PI's Guide to Conducting Clinical Research* provides an overview of GCP rules principal investigators encounter most often.

GCP Regulations and Guidance

In order to conduct high-quality, compliant clinical trials, investigators must have a thorough understanding of the regulations and relevant guidances that govern study conduct, as well as of the overall 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—Applications for FDA Approval to Market a New Drug
- 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 is actually 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 website. Some of the more useful guidances include:

- Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

- Informed Consent Information Sheet
- Exception from Informed Consent Requirements for Emergency Research
- Recruiting Study Subjects
- Clinical Investigators — Disqualification Proceedings
- Using a Centralized IRB Review Process in Multicenter Clinical Trials

FDA Compliance Program Guidance Manuals

There are also 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 Investigators
- CPGM 7348.810 for Sponsors, Monitors and Contract Research Organizations
- CPGM 7348.809 for IRBs

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 trial, 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.

FDA Bioresearch Monitoring Program

The 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 that GCP standards are followed, the FDA inspects clinical trials. The FDA calls these “inspections,” although others call them “audits.” The FDA's program of clinical trials inspections 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 should be familiar with the International Council on Harmonisation (ICH) guideline for good clinical practice, ICH E6.

Although not considered regulation in the U.S., this guideline was originally published in 1996 and updated in 2016. It represents the FDA's thoughts on good clinical practice (i.e., an FDA final guidance document). In addition, the elements of ICH E6 have been adopted into the EU's Clinical Trial Directive, a set of laws that govern the conduct of EU clinical research.

GCP is derived from the federal regulations, ethical codes, ICH guideline and other official guidance documents. GCP evolved because of concerns about the treatment of human participants in research around the world, and the reliability of the data and conclusions from trials. Concern about data and conclusions goes beyond the need to protect patients in clinical trials, extending to the greater goal of protecting all future patients who will receive these potential pharmaceutical or biological products. There are serious consequences for not following GCP regulations and laws, including loss of revenue and loss of reputation. The failure to follow GCP can expose research sponsors, clinical investigators and institutions to serious concerns about potential legal liability, not only from study participants, but from future health consumers (e.g., class action suits).

The International Organization for Standardization (ISO) represents medical device standards bodies in more than 160 countries, including the U.S. ISO 14155, *Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice* is an FDA-recognized standard. The same regulatory and ethical imperatives that were the impetus for the ICH GCP guideline apply to ISO 14155.

The U.S. Common Rule, first published in 1981 and updated in 2017, is a multi-agency document that sets out standards for protecting human subjects involved in research. It applies any time human subjects research is conducted using federal funding; therefore, federal agencies, academic institutions and healthcare research institutes are among the top qualifying institutions. Included in the updates to the Common Rule, frequently referred to as the "Final Rule," are new requirements for informed consent, the delineation of several new and expanded exempt categories of research, the creation of a new classification of "broad consent," the introduction of limited Institutional Review Board review, the discontinuation of "continuing review," and an update to the description of vulnerable populations, in addition to other changes.

Electronic Records and Electronic Signatures

On occasion, a sponsor may require electronic records, electronic data collection and/or the use of electronic signatures during a study. In this case, the investigator must ensure that all sponsor requirements and all regulatory requirements regarding electronic records and signatures are followed. All site personnel involved in electronic records, electronic data collection and/or electronic signatures should be familiar with the regulations found in 21 CFR Part 11.

Investigators may rely on the sponsor to ensure compliance with Part 11 as it pertains to eCRFs, but it is the investigator's responsibility to ensure Part 11 compliance when an EMR is used, including those that permit electronic signatures to validate the accuracy of entries in that EMR. A May 2007 FDA guidance document. *Computerized Systems Used in Clinical Investigations*, expresses the FDA's expectations for EMRs, and medical records departments should be familiar with this guidance document.

The Health Insurance Portability and Accountability Act (HIPAA)

Our healthcare system relies increasingly on the rapid and widespread exchange of printed and electronic patient information. In an effort to protect individuals' rights to control access to and disclosure of private and confidential information, and to ensure the continuity of coverage between health insurance plans, the Federal government passed the Health Insurance Portability and Accountability Act (HIPAA) in 1996 and implemented the HIPAA Privacy Rule in April 2003.

Under the Code of Federal Regulations (45 CFR Parts 160 and 164), the HIPAA Privacy Rule has a far-reaching and significant impact on the clinical research process. The Privacy Rule essentially pertains to all clinical research studies that utilize identifiable personal health information, including study volunteers' name, address, phone number, fax number, email address, license plate, Social Security number, medical record number, health plan beneficiary number, data from laboratory work/tissue samples and photographic images. A small percentage of phase 1 studies of healthy participants may fall outside the scope of HIPAA.

The HIPAA Privacy Rule applies to the uses and disclosures of protected health information (PHI) specifically by healthcare providers, health plans and healthcare clearinghouses (covered entities). All clinical investigators, including those who are not otherwise part of these covered entities, must comply with the Privacy Rule when any of their clinical trials involve medical treatments. Investigators also must comply with the HIPAA Privacy Rule if they request PHI from covered entities.

Institutions and independent sites conducting clinical trials were required to begin their full compliance with the HIPAA Privacy Rule on April 14, 2003. Failure to comply may result in costly fines, as well as civil, or even criminal, sanctions against an institution or site.

All study staff must make reasonable efforts to use or disclose only the minimum necessary information about their study participants. Clinical staff can review a participant's complete medical records and share information freely with other clinicians directly involved with that patient's care.

However, under the HIPAA Privacy Rule, clinical investigators also must obtain authorization from study volunteers in order to use and disclose their identifiable and protected health information. During a clinical research project, study participants' medical records and signed consent forms will be reviewed and even copied for scientific and regulatory purposes. Information from the study will be given to the company sponsoring the research. This information also may be given to the FDA and other regulatory agencies in countries where the test article is being considered for approval.

Unless an exception applies, or an IRB has approved a waiver, clinical investigators may not use or disclose any protected health information without first obtaining signed authorization from study volunteers. The authorization form used, if it is incorporated into the informed consent form, must be approved by an IRB prior to reviewing it with study participants. The authorization form must identify the parties that can use and disclose the PHI, as well as the parties to whom the PHI may be disclosed. It also must provide study volunteers with information related to their rights and recourse, and how their information may be used and disclosed. HIPAA authorization may be incorporated into the body of the informed consent form, or it may be provided through the use of a separate authorization document. IRB approval may not be required for a separate authorization form, although organizational policy may vary.

The HIPAA regulations cover any patient information at a site that could be used to identify the person to whom the information pertains. This PHI includes, but is not limited to, the following items:

- Names
- Addresses (any geographic subdivisions smaller than a state)
- Employers' names or addresses
- Relatives' names or addresses

- All elements of dates related to a person except for year
- Telephone numbers
- Fax numbers
- Email addresses
- Social Security numbers
- Medical record numbers
- Certificate numbers (including device serial numbers for implants)
- Member or account numbers
- Certification/license numbers
- Voiceprints
- Fingerprints
- Vehicle identifiers
- Device identifiers
- Biometric identifiers
- Full face photographs
- Any other unique identifying number, characteristic or code.

There is a difference between the terms "use" and "disclosure" of PHI. HIPAA regulations define these terms in the following way. "Use" happens within a healthcare organization and is under the direct control of the organization; for example, a nurse in a clinic "uses" PHI. "Disclosure" occurs when the PHI is given to someone who is not part of the organization (not an employee); for example, allowing a sponsor's monitor (CRA) to see a study participant's office chart/source documents.

For information on *The PI's Guide to Conducting Clinical Research*, click here: https://bit.ly/2y0ErH2.