

The standards on "Good Clinical Practice" developed by the [International Conference on Harmonization](#) "is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the [Declaration of Helsinki](#), and that the clinical trial data are credible." (62 FR 25693). Any investigator performing a clinical trial involving a drug, biologic or device should conduct the trial in accordance with the [Good Clinical Practice](#) standard. This module will focus on drug studies, with the same standards applying to the full range of clinical pharmaceutical development from phase 1 through phase 4 investigations.

Prior to drug approval, an Investigational New Drug Application is required to start clinical studies and must be submitted to the FDA at least 30 days prior to the start of the research. As part of this application, the investigator must submit [Form 1572](#) which outlines the responsibilities that the investigator agrees to assume in order to conduct the study. Clearly, the investigator must have sufficient time and scientific interest to meet these responsibilities, and the ability to meet the recruitment targets and not have any competing trials. It is unlikely that an investigator will be sufficiently motivated to ensure compliance with the "Good Clinical Practice" responsibilities if the sole interest in performing the research is financial.

The following discussion is organized according to the nine commitments that the investigator affirms in filling out the FDA Form 1572. This is not a complete discussion of the "Good Clinical Practice" guidelines. An investigator contemplating pharmaceutical research should consult the FDA Web site for a list of relevant documents.

*"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." (FDA Form 1572)*

Section 4.5 of the [GCP guidelines](#) states that the trial should be conducted in compliance with the approved protocol. The investigator should not deviate from the protocol in any manner without the agreement of the sponsor and the prior review and documented approval of the IRB. The only exception is when the change or deviation from the protocol is necessary "to eliminate an immediate hazard(s) to trial subjects." If such an event occurs, the investigator should submit as soon as possible a written justification for the implemented deviation or change to the IRB (along with a proposed protocol amendment, if appropriate), the sponsor and, if required, the FDA.

*"I agree to personally conduct or supervise the described investigation(s)."  
(FDA Form 1572)*

The GCP guidelines stipulate that the investigator should have sufficient time to properly conduct and complete the trial (4.2.2), should be able to demonstrate the potential for recruiting the required number of suitable subjects (4.2.1), and should be "qualified by education, training, and experience to assume responsibility for the proper conduct of trial" (4.1.1).

"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." (FDA Form 1572)

The GCP guidelines state that "the rights, safety, and well-being of trial subjects are the most important considerations and should prevail over interests of science and society" (2.3). The requirements for written informed consent found in section 4.8 are consistent with 45 CFR 46 and 21 CFR 50, although there are some specific requirements related to industry-sponsored research which will not be discussed in this module. The GCP guidelines require that the informed consent document "be revised whenever important new information becomes available that may be relevant to the subject's consent" (4.8.2). Also, the IRB is specifically required to review "both the amount and method of payment to subjects to assure that neither presents problems of torsion or undue influence" (3.1.8).

The IRB is specifically charged with paying special attention to trials that may include vulnerable subjects. The definition of "vulnerable subjects" is worthy of emphasis. Vulnerable subjects are defined as "individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchal structure, such as a medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the Armed Forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent" (1.61).

"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](#)." (FDA Form 1572)

The definitions of adverse drug reaction, adverse event, serious adverse event or serious adverse drug reaction, and unexpected adverse drug reaction are given below. The investigator is required to promptly report to the IRB all adverse drug reactions that are both serious and unexpected (3.3.8c). The investigator is required to promptly report to the sponsor all serious adverse events regardless of whether or not they are unexpected, except for those serious adverse events that are identified in the protocol or other documentation as not needing immediate reporting (4.11.1). Other adverse events and/or laboratory abnormalities that are identified in the protocol as critical to the evaluation of the safety of the investigational product should be reported to the sponsor as outlined in the protocol (4.11.2). The sponsor is also under a similar obligation to report both serious and unexpected adverse drug reactions to all concerned investigators, institutions, IRBs, and the FDA (5.17.1).

Adverse Drug Reaction (ADR): "all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase 'responses to a medicinal product' means that a causal

relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out" (1.1)

Adverse Event (AE): "An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product" (1.2).

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR): "Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect" (1.50).

Unexpected Adverse Drug Reaction: "An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)" (1.60).

"I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug." (FDA Form 1572)

The GCP guidelines stipulate that the investigator "should be thoroughly familiar with the appropriate use of the investigational product(s)" as described in the protocol and other supporting documentation. (4.1.2) The investigator takes the responsibility to be considered an expert in the use of the investigational product.

"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." (FDA Form 1572)

Although the investigator may delegate "significant trial related duties" (4.1.5), it is the investigator's responsibility to make sure that "each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)" (2.8). In addition to providing "an adequate number of qualified staff and adequate facilities... to conduct the trial properly and safely" (4.2.3), the investigator is responsible for ensuring that "all persons assisting with the trial are adequately informed about the protocol, investigational product(s), and their trial related duties and functions" (4.2.4).

"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](#)." (FDA Form 1572)

The best research is useless without a data collection and storage process that assures "accurate reporting, interpretation, and verification" (2.10). FDA regulations require the investigator "to prepare and maintain adequate and accurate case histories that report all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation" (21 CFR 312.62b). The GCP guidelines provide a detailed list of those documents that should be located in

the files of the investigator before, during and after the completion of a clinical investigation ([62 FR 25705-25709](#)). Among the documents that the investigator must maintain include:

- the investigator's brochure,
- the signed protocol and amendments,
- the approved informed consent form and
- any other written information or advertisements used for subject recruitment,
- financial and contractual agreements,
- all IRB correspondence,
- documentation that the IRB is constituted in agreement with GCP guidelines,
- curriculum vitae and/or other documentation as evidence of investigator(s) qualifications,
- certification of "good laboratory practices" for testing facilities,
- labeling, shipping and handling instructions for the investigational product,
- any updates or revisions to the above material,
- monitoring visit reports,
- study-related communications,
- signed informed consent forms,
- source documents that substantiate the integrity of the data,
- signed, dated and completed case report forms,
- reports of serious adverse events and unexpected serious adverse drug reactions and other safety information,
- progress or continuing reports submitted to the IRB and/or the FDA, and
- the final monitoring report and clinical study report documenting the completion, results and interpretation of the trial.

"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." (FDA Form 1572)

The CHOP IRB functions in compliance with [45 CFR 46](#) and [21 CFR 56](#). The GCP guidelines requires the investigator to submit the appropriate documentation for both initial and continuing review, as well as ongoing information about the safety of the trial. In addition, the investigator will provide "any of the documents that the IRB may require to fill its responsibilities" (3.1.2). The investigator should consult the Stokes Intranet under the Office for Research Regulatory Affairs to review the most recent policies concerning document submission and to obtain the appropriate and most recent forms.

"I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312." (FDA Form 1572)

Clinical trials that are under the regulatory authority of the FDA are subject to auditing. There are approximately 200-300 study-directed audits performed per year. In addition, the FDA conducts approximately 30-40 investigator-directed audits per year. During the audits, the FDA checks compliance with FDA regulations, protocol adherence, and institutional operating procedures. The FDA will audit investigator's study file and the IRB documentation to determine

compliance with all of the investigator responsibilities as outlined on Form 1572.

The most common deficiencies that are identified by FDA audits include:

- problems with informed consent (51 percent);
- inadequate drug accountability (20 percent);
- protocol violations (31 percent);
- inadequate and inaccurate records (26 percent);
- IRB deficiencies (11 percent); and,
- investigator failure to report adverse events.

Investigator disqualifications have resulted from:

- repeated and delivered submission of false data;
- failure to obtain IRB approval;
- failure to obtain informed consent;
- failure to sign Form 1572;
- failure to follow protocol;
- inadequate record-keeping;
- failure to administer the study drug; and,
- refusing to allow FDA inspection.

The results of [FDA inspections](#) in 1997 included eighty-three disqualifications, 34 restrictions, and 17 prosecutions/convictions. Finally, if the investigator discovers noncompliance with any aspect of the conduct of the clinical investigation, this must be reported to the IRB, to the sponsoring agency, and in some cases the FDA.

In concluding this module, it is worth repeating the purpose for the development of the "Good Clinical Practice" guidelines and the importance of investigator compliance with the above standards. "Compliance with Good Clinical Practice provides public assurance that the rights, well-being, and confidentiality of trial subjects are protected and that trial data are credible" (62 FR 25692). Our ability to conduct clinical research is a privilege that is granted to us by the trust of research participants and of society in the worthiness of the research endeavor. Our compliance with the standards of "Good Clinical Practice" earns this public trust.