

# ASHP Guidelines on Clinical Drug Research

## Purpose

The use of drug products to manage diseases and improve patients' quality of life is increasing as more effective and safer agents become available. Research to develop these agents is occurring in health system practice settings throughout the world. The credibility of this research and the protection of human subjects is a major responsibility of all health professionals involved.

ASHP believes pharmacists should play a pivotal role in the management of drugs used in the conduct of clinical research.<sup>1-3</sup> Pharmacists have become essential components of health system infrastructures supporting clinical research with both approved drugs and investigational drugs.<sup>a,b</sup> Pharmacists' roles in clinical research generally fall into one of two categories: (1) drug storage, preparation, and record keeping, frequently through an investigational drug service, and (2) serving as a principal investigator or a subinvestigator, manager, or coordinator within a research team that may include other health care professionals, research sponsors, monitors, contract research organizations, institutional review boards (IRBs), and institutional administrators.

The purposes of this document are to (1) outline the principles of clinical research, (2) describe the roles of participants in clinical research, (3) define pharmacists' roles in the use of drugs in clinical research, and (4) provide guidance to pharmacists and others responsible for the medication management component of clinical research. ASHP believes these guidelines are applicable to clinical research conducted in any health-system practice setting. These guidelines are an interpretation of federal laws, regulations, and standards for pharmacy practice in health systems. They should be used in conjunction with the applicable federal and state laws and regulations, not as a substitute for them. This document uses the term *shall* when the content is based on law or regulation and the term *should* for advice based on other guidelines, professional judgment, or expert opinion.

## Background

The United States has benefited from a system for researching and marketing drug products that is codified in federal and state laws and regulations. The federal Food, Drug, and Cosmetic Act and its amendments<sup>4</sup> regulate drug product quality, safety, and effectiveness. The Food and Drug Administration (FDA) is the federal agency charged with enforcing the act and promulgating regulations for its implementation. FDA regulations concerning the conduct of clinical research with drug products of particular relevance for health-system pharmacists include Title 21 Code of Federal Regulations (CFR) Part 50, Protection of Human Subjects; Title 21 CFR Part 56, Institutional Review Boards; and Title 21 CFR Part 312, Investigational New Drug Application. Also applicable are the Department of Health and Human Services regulations in Title 45 CFR Part 46, Protection of Human Subjects. Requirements for and guidance on compliance with regulations are provided in FDA Information Sheets.

FDA has also published the Good Clinical Practice Consolidated Guideline<sup>5</sup> that was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals

for Human Use. The guideline offers a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects in the United States, Japan, and the European Union. In particular, the guideline provides a clearer understanding of behavioral and compliance standards for regulated drug research.

## Basic Principles

The institutional components and practice settings of health systems participating in clinical drug research shall develop mechanisms, generally in the form of policies and procedures, for the approval, planning, and implementation of protocols. Good clinical practices, consistent with national and international standards, are the cornerstone of drug research in humans. Principles consistent with good clinical practices include the following:

1. An organization participating in human drug research studies shall ensure that such studies contain adequate safeguards for human subjects, its staff, and the scientific integrity of the study. There shall be written policies and procedures for the approval, management, and control of research involving investigational (not FDA-approved) drugs and post-marketing studies of FDA-approved drugs used in a research protocol. All research team members shall be fully informed about and comply with these policies and procedures.
2. The clinical trial shall have adequate prior information to justify use of human subjects, have a clearly defined protocol, and have received IRB approval before implementation.
3. All drug studies shall meet accepted ethical, legal, and scientific standards and be conducted by appropriately qualified investigators. Investigator qualifications, such as prior training and experience in research and with certain disease states, are required to be reviewed by IRBs, study sponsors, and FDA if the research will be submitted under an investigational new drug application (IND).
4. Every member of the research team shall be qualified by experience or training to perform his or her respective role.
5. All subjects must freely provide informed consent (documented in writing) before treatment with study drugs is begun. Accurate and complete information about the study's objectives, risks, and benefits must be provided before consent is obtained from the subject or his or her legally authorized representative. No unreasonable inducements (i.e., coercion or undue influence) shall be offered to subjects to encourage their participation in the study.
6. All clinical trial data shall be recorded and the records stored in such a way that the subject's rights of privacy and confidentiality are protected. All records shall be managed in a way that permits accurate reporting, verification, and retrieval after archiving.
7. Qualified pharmacists and other nonphysicians may serve as principal investigators as long as medical decisions made for the subjects are always the responsibility of a qualified physician or dentist.

## Health-System Organization and Oversight

The health system should have processes for the administration of research that ensure that the aforementioned principles are upheld and the following responsibilities are met.

1. The health system shall be able to review and approve a protocol in the context of federal, state, and local laws and regulations. The health system should consider whether its own sponsored research or intellectual property development of drugs requires an IND for drugs not commercially available and approved drugs for unlabeled uses. An IND may be required if proposed research on the use of a marketed drug is intended to support the sponsor's change in drug labeling, advertising, or indications for use; a significant increase in risk; or a change in dosage level or route of administration. The health system should consult FDA for guidance.
2. The health system should have a mechanism for review and approval of the financial aspects of drug research, whether the study is sponsored by government agencies, foundations, or the pharmaceutical industry or is not sponsored.<sup>6</sup> Financial aspects may include contractual agreements stipulating cost recovery for resources, intellectual property agreements, insurance provisions, indemnification terms, and conflict-of-interest statements. Cost identification, allocation, and recovery mechanisms are imperative items for review and approval.
3. As required by federal regulation, clinical research shall be reviewed and approved by an IRB or equivalent committee (21 CFR 56.109). This committee shall evaluate each proposed clinical research study in terms of human subject protections and compliance with recognized ethical, legal, and scientific standards. No clinical study may be initiated unless approved in writing by the committee. Spoken IRB approval may be granted in emergency situations for a single subject's access to an investigational drug, but emergency use shall be reported to the IRB within five days; subsequent use requires full IRB review. Studies on the use of drugs in emergency or critical care settings do not in themselves qualify for single-subject approval and emergency exemption. Specific regulations govern research in the emergency setting and should be consulted in preparing protocols, IRB submissions, and consent procedures.<sup>c,7</sup>

Treatment IND protocols are also subject to IRB review and approval. These protocols permit patient access to investigational drugs through a special program established by a sponsor. The physician and patient must agree that use of the agent may be in the patient's best interest and must document this agreement on a consent form.

The IRB shall monitor approved studies to ensure that they are carried out appropriately and that the protocols are reassessed at least annually. Health system policies and procedures shall provide guidance on the conversion of human subjects to other therapies in the event that approval of an existing protocol is withdrawn by the IRB. The investigational-drug pharmacist, pharmacy director, or pharmacy director's designee should be a member of the IRB and should be consulted by the committee whenever drug studies are reviewed.

4. Investigational drugs shall be used only under the supervision of the principal investigator or authorized subinvestigators, all of whom shall be members of the professional staff. The determination of qualifications for investigators is the responsibility of the sponsor, IRB, and FDA when appropriate. Properly qualified pharmacists with experience and training in research may serve as principal investigators or subinvestigators.
5. The principal investigator or designee is responsible for obtaining informed consent from each subject who is eligible for participation in the study (i.e., meets inclusion and exclusion criteria).<sup>c</sup> The informed consent process shall conform to current federal and state regulations. IRB approval of the consent form (and assent form for minors) is required. Review by legal counsel may be desirable. The following points shall be included in the consent document and in an accompanying oral explanation by the investigator:
  - a. That the trial involves research.
  - b. The nature and purpose of the study and its expected benefits and foreseeable risks or discomforts. The name and telephone number of the principal investigator and persons to contact for questions about the study or drug.
  - c. A balanced description of the alternative treatments available, including their respective risks and benefits.
  - d. A general description of the study procedures, identification of any procedures that are experimental, expected length of therapy with the drug, and the subject's responsibilities. The name(s) of the investigational drug(s), including brand and generic names of commercial products.
  - e. A statement that (1) participation is voluntary, (2) the subject may withdraw from the study at any time, (3) refusal to participate in or withdrawal from the study will involve no penalty or loss of benefits to which the subject is otherwise entitled, and (4) the principal investigator may remove the subject from the study if circumstances warrant. The investigator shall supply any new information that may affect a subject's desire to continue in a study.
  - f. The name and signature of the subject (or his or her legally authorized representative), the name and signature of the principal investigator or subinvestigator, and the name and signature of the person presenting the consent form, with lines for each to personally date the signature.
  - g. A statement of who will have access to any study records that contain subject identifiers, including monitoring personnel from the study sponsor or FDA who may inspect the records to assess compliance with the study protocol and all regulations, or institutional personnel auditing the quality of clinical research or financial transactions.
  - h. Compensation or treatment available for a research-related injury.
  - i. Anticipated payments to subjects, pro rata terms, or expenses subjects may incur. Any costs for which the subject will be responsible.

The consent form shall be as detailed as is practical, with the goal of minimizing the amount of information that must be presented orally yet enabling

comprehension by most persons reading the form. For non-English-speaking subjects the consent form shall be in the subject's own language when feasible, or adequate interpretation shall be provided. For children able to read, an assent form shall be used to document their participation in the research process. The subject (or his or her representative) must have adequate time to read the consent form before signing it and shall receive a copy of the signed and dated form, along with any amendments to it. The subject shall retain a copy of the consent form. Additional copies of the consent form shall be kept on file as required by the sponsor, the IRB, the individual health system, and the medical records department.

Under certain protocols, patient drug or medical information may be collected from existing medical or pharmacy records. Pharmacists and investigators should consult the IRB to determine protocol-review and informed-consent requirements for any proposed studies.

6. The principal investigator is responsible for the proper maintenance of case report forms and all other study records required by the health system, the sponsor, and FDA.
7. The health system's medication-use system shall contain the following elements concerning drugs used in clinical research:
  - a. Drugs shall be properly packaged in accordance with all applicable federal and state laws, regulations, and standards (e.g., FDA, *The United States Pharmacopeia and The National Formulary [USP-NF]*, and the Poison Prevention Packaging Act).
  - b. Drugs shall be labeled properly to ensure their safe use by the research and institutional staff and the subject.
  - c. There shall be a mechanism to ensure that sufficient supplies of the drugs will be always available for the duration of the study.
  - d. A mechanism shall be in place to allow the pharmacist or other designated health care provider, in a medical emergency during a randomized and blinded trial, to break the blinding code and reveal the identity of the study drug to other health care professionals. A reason to break the blind might be the need for a treatment decision that can be made only with knowledge of drug assignment.
  - e. Nurses, pharmacists, physicians, and other health care practitioners (e.g., respiratory therapists, physician assistants) called on to administer or dispense investigational drugs should have adequate written information about (1) pharmacology (particularly adverse effects), (2) storage requirements, (3) method of dose preparation and administration, (4) disposal of unused drug, (5) precautions to be taken, including handling recommendations, (6) authorized prescribers, (7) human subject safety monitoring guidelines, and (8) any other material pertinent to safe and proper use of investigational drugs. These health care providers should be informed about the overall study objectives and procedures and shall have available a complete copy of the protocol for reference. Under all circumstances, investigational drugs shall be safely controlled, administered, and destroyed.
- f. Bulk supplies of the investigational drug shall be properly stored and adequately secured. When practical, all bulk supplies shall be stored in the pharmacy to ensure that storage, dispensing, accountability, and security are in compliance with federal and state laws and regulations and with standards used by the pharmacy department.
- g. There shall be a method for ensuring that only an authorized practitioner or designee prescribes the investigational drug.
- h. Records of the amount of investigational drug received from the sponsor and of its disposition (e.g., amounts dispensed to subjects or returned to sponsor) shall be maintained. These records shall be retained as required by regulation. Generally, records shall be maintained for at least two years after the date of an approved new-drug application (NDA) for the indication that is being investigated or, if the application is not approved or no application is filed, for at least two years after the investigation is discontinued and FDA is notified. Institutions should consider retaining records indefinitely. For studies involving international sites, records shall be maintained for 15 years after study closure. The sponsor may also request that records be stored longer than the minimum required time.
- i. If the subject is to receive the investigational drug at another facility, suitable arrangements shall be made for transfer of the drug. Sufficient information for safe use of the investigational drug, including copies of the subject's signed consent form, the study protocol, and the IRB approval letter, shall accompany the drug. The responsibilities of the facility to which the drug is transferred are based on whether that facility is providing care incidental to or as a participant in the research protocol.<sup>8</sup>
- j. The institution's records on investigational-drug studies should be designed so that various descriptive reports (e.g., names of all drugs under study, names of subjects who have received a given drug) can be generated conveniently and expeditiously. Once a study is closed, a copy of all pharmacy-related records should be provided to the principal investigator for storage. For its own records, the pharmacy should have a mechanism for long-term storage. The drug control responsibilities previously described shall be assigned to a pharmacist. If a pharmacist is not available, the investigator shall make arrangements to comply with these standards.

## Pharmaceutical Services

A pharmacist should be responsible for ensuring that procedures for the control of drugs used in clinical research are developed and implemented. Each health system should develop a structure and procedures specific to its own needs and organization.

1. A copy of the IRB-approved research protocol and investigator's brochure or drug data sheet (see item 2 below), or both, and all amendments should be kept by a pharmacist.
2. Using the protocol and additional information (if needed) supplied by the principal investigator and sponsor, the pharmacist should prepare an investigational-drug data

sheet that concisely summarizes for the medical, nursing, and pharmacy staffs information pertinent to use of the drug. This communication should contain, at a minimum

- a. Drug designation and common synonyms.
  - b. Dosage forms and strengths.
  - c. Usual dosage range, including dosage schedule and route of administration.
  - d. Indications pursued in this study.
  - e. Expected therapeutic effect to be studied.
  - f. Expected and potential adverse effects, including symptoms of toxicity and their treatment.
  - g. Drug-drug and drug-food interactions.
  - h. Contraindications.
  - i. Storage requirements.
  - j. Instructions for dosage preparation and administration, including stability and handling guidelines.
  - k. Instructions for disposition of unused doses.
  - l. Names and telephone numbers of principal and authorized subinvestigators and study coordinators.
- Confidential copies should be distributed to the appropriate pharmacy staff and all areas within the health system where the investigational drug will be administered and the subjects monitored. Through the pharmacy or health-system computer system, this information can be made available to all staff members who need it. It is staff members' responsibility to become familiar with the information in these data sheets and to not share the information with persons who do not need it.
3. When it is practical, investigational-drug supplies should be stored in a pharmacy. When the drug is stored outside a pharmacy (e.g., small quantities in the investigator's office or in clinics where the drug is administered), methods used by the investigator responsible for the drug shall be audited by a pharmacist to ensure that storage, dispensing, accountability, and security comply with federal and state laws and regulations and with institutional policy.
  4. The pharmacist shall maintain a perpetual inventory record for investigational drugs stored in the pharmacy. This record shall contain the drug's name, dosage form and strength, lot number, and expiration date; the name, address, and telephone number of the sponsor; the protocol number; and any other information needed for ordering the drug. Space shall be provided for recording data on the disposition of the drug (amounts received, transferred, wasted, or dispensed, with dates; the names of or codes for persons receiving the drug; and the names of prescribers), the amount currently on hand, the minimum reorder level, and the recorder's initials. The inventory record shall reflect drug doses that were dispensed but not administered and were returned to the pharmacist. These records are commonly audited by the sponsor, the sponsor's representatives, or FDA.<sup>9,10</sup>
  5. The dispensing of investigational drugs should be integrated with the rest of the medication-use system, including, but not limited to, order review, profile maintenance, packaging, labeling, delivery, and quality-assurance procedures. However, prescription labels for investigational drugs shall be marked "investigational drug" or otherwise distinguished from other labels. The label should also include an alert to any

possible hazards. There shall be a method for verifying that a valid, signed consent has been obtained. The investigational drug shall be dispensed only on the order of an authorized investigator or designee.

6. Educating patients and monitoring therapy (including adverse drug reaction monitoring) are two clinical functions that are particularly important and applicable to investigational drugs. The protocol should specify the provision of these functions by the pharmacists, the authorized investigator(s), and other members of the research team.
7. At the conclusion of the study, the pharmacist shall return, transfer, or dispose of all unused investigational drugs according to the specific instructions provided by the sponsor and in accordance with applicable regulations.
8. The pharmacist should prepare an annual or semiannual descriptive summary of investigational-drug use for the pharmacy director and pharmacy and therapeutics committee. This summary should include the number of studies in progress, a list of all drugs studied during the previous period, and a financial statement.
9. Drug costs and other expenses associated with drug studies (e.g., costs of record keeping and drug administration) should be properly allocated and reimbursed. Policies and procedures should address the role pharmacists play in billing sponsors, subjects, and third-party payers for services and goods related to research. In general, sponsors and health systems cannot charge subjects for an investigational drug. Sponsors may petition FDA for an exception. Health systems may charge subjects for drug preparation and other services necessary to deliver a final product, as is customary for delivery of services within the practice setting and when sponsors do not reimburse for this service. The anticipated costs of research should be described in the consent form. Subjects must be advised that they or their third-party payers are responsible for these charges and that a third-party payer may refuse to pay for charges related to research.
10. The investigational drugs shall be stored under appropriate environmental control in a limited-access area separate from routine drug stocks and shall be inventoried on a regular basis.
11. Pharmacists may be confronted with circumstances related to a patient who is receiving an investigational drug provided by an investigator at a nonaffiliated practice setting and is admitted to their own practice setting for care incidental to the research protocol. Pharmacists should have a policy for managing investigational drugs under those circumstances that meets FDA guidelines.<sup>8</sup>
12. Pharmacists must ensure the scientific integrity of drug studies by managing access to treatment-assignment records in blinded studies and by ensuring that the correct drug was dispensed. The pharmacist, investigator, and sponsor must agree on a procedure for unblinding treatment assignment in emergencies.
13. Pharmacists who are assigned to manage investigational drugs may at times have to delegate certain dispensing activities to other pharmacists within the health system. To ensure continuity of quality dispensing services, the responsible pharmacist should design and implement procedures for educating other members of the pharmacy

staff about the protocol and dispensing requirements. Often this can be accomplished by personal instruction and by preparing written directives and references for use by other pharmacists when they are called upon to dispense an investigational drug.

14. Pharmacists managing investigational drugs are in a unique position to monitor patient adherence to medication regimens. Because of the requirement that medication dispensed and returned be accounted for, pharmacists can readily surmise whether study patients are consuming the medication in the prescribed manner. At a minimum, pharmacists should counsel the investigator's research staff with regard to patient adherence. Pharmacists' skills in patient counseling should be used to support the investigators' efforts to encourage patients to adhere to their protocols.

### Pharmaceutical Research Sponsors, Monitors, and Contract Research Organizations

The pharmaceutical company, or any study sponsor, that supports the use of investigational drugs in health systems should receive reliable and valid data. The following recommendations will serve as a guide to the pharmaceutical industry or other study sponsors to ensure that investigational drug use is managed appropriately and that studies are conducted effectively, efficiently, and safely.

1. Drugs shall be properly packaged in accordance with all applicable federal and state laws, regulations, and standards (e.g., FDA, *USP-NF*, and the Poison Prevention Packaging Act).
  2. Drugs shall be properly labeled in accordance with applicable laws, regulations, and standards. If possible, ample space shall be left on the drug product container for further labeling by the pharmacist. Expiration dates and lot numbers should also be noted on the label.
  3. A 24-hour telephone number should be available to study personnel, including the principal investigator and the pharmacy department. In the event of an emergency, information should be available pertaining to (1) adverse effects and their treatment, (2) emergency protocol management and dosing and administration guidelines, (3) the ability to break a "blinded code" to determine the treatment regimen, and (4) the mechanism for procuring a supply of medication under an emergency-use protocol.
  4. Company representatives should be designated to handle routine requests, such as those for additional forms and resupply of investigational drugs. If possible, direct telephone or fax access should be available to expedite requests.
  5. Investigational drugs should be shipped to the principal investigator in care of a pharmacist. The following information about procurement should also be supplied to the pharmacist:
    - a. Name and telephone number of the sponsor's study monitor or field representative responsible for drug ordering.
    - b. Estimated time for fulfillment of orders.
    - c. Limits on quantities that can be ordered.
    - d. Special ordering instructions.
  - e. How the order is to be shipped (e.g., specific package-shipping firms).
  - f. Disposition of invoice or drug receipt form once the drug is received.
6. The following information should be supplied by a sponsor or investigator to the pharmacist, preferably in an investigator's brochure, as applicable:
    - a. Storage conditions required before and after preparation.
    - b. Amounts and types of diluents for reconstitution and administration and the resulting final concentration of active drug.
    - c. Stability of the prepared (i.e., ready-to-administer, reconstituted, or diluted) product and compatibility with drug delivery systems, diluents or i.v. fluids, containers, i.v. tubing, and filters.
    - d. Known compatibility or incompatibility with other products.
    - e. Light sensitivity.
    - f. Filtration needs.
    - g. Expiration dates or retest dates.
    - h. Special instructions for preparation and administration.
    - i. Acceptable and recommended routes and methods of administration, including rates of infusion for injectable products.
    - j. Known adverse effects during or after administration (e.g., pain, phlebitis, and nausea) and how to avoid and treat them.
    - k. Usual dosage regimens and highest dose tested for specific disease states, including dosage expressions for prescribing and labeling that could minimize misreading and misinterpretation.
    - l. Contraindications.
    - m. Drug interactions.
    - n. Special precautions for storage, handling, and disposal of the drugs, including cytotoxic and hazardous drugs. For all hazardous drugs, the pharmacy department must be supplied with material safety data sheets.
    - o. Pharmacology, including mechanism of action.
    - p. Pharmacokinetic characteristics.
  7. If all unused drugs are to be returned to the sponsor, information regarding storage and return procedures should be provided to the pharmacist. Drugs that are contaminated, outdated, or otherwise unsuitable should be returned to the sponsor or destroyed according to the institution's policies and procedures and applicable laws and regulations. These options should be agreed on beforehand by the sponsor and the pharmacist.
  8. A complete current copy of the research protocol and investigator's brochure should be supplied to the pharmacist. Additional educational materials for use in informing pharmacists, physicians, and nurses about the investigational drug and research protocol should also be provided.
  9. An appropriate allotment of research funds should be designated as reimbursement for
    - a. Personnel.
    - b. Storage facilities.
    - c. Equipment.
    - d. Ancillary products, such as diluents, syringes, and needles.
    - e. Forms and miscellaneous clerical materials.

- f. Computer and other data-processing costs.
  - g. Other expenses attributable to the pharmacist's involvement in the study.
  - h. Apportioned pharmacy overhead costs.
10. Sponsors should respond to requests for information from pharmacists involved in treating patients without formal research approval at that institution. This may occur, for example, when a patient is hospitalized (e.g., in an emergency) at a facility other than his or her usual care site.
  11. When seeking marketing approval for an investigational drug, sponsors should consult pharmacists, physicians, and others involved in their investigational-drug studies for information. Because of their experience with the drug, these practitioners can supply valuable suggestions for labeling, packaging, palatability, routes of administration, and other dosage form characteristics, as well as information regarding patient monitoring and education.
  12. The sponsor of an investigational drug study should provide final closure details within six months of trial completion. This includes prompt notification of closure, directions for drug disposition, and final audits of all study records.
  13. These recommendations should also apply to the postmarketing approval of drugs under study for new indications or diseases.

## References

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## Suggested Internet Source

Food and Drug Administration information for clinical investigators. [http://www.fda.gov/cder/about/smallbiz/clinical\\_investigator.htm](http://www.fda.gov/cder/about/smallbiz/clinical_investigator.htm).

## Glossary<sup>d</sup>

**Adverse Drug Reaction (ADR):** In preapproval clinical experience with a new medicinal product or its new usages, particularly since the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. "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., that the relationship cannot be ruled out).

An ADR to a marketed medicinal product is a response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

**Adverse Event (AE):** An AE is any untoward medical event that occurs in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship to 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.

**Audit:** A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures, good clinical practice, and the applicable regulatory requirements.

**Audit Report:** A written evaluation by the sponsor's auditor of the results of the audit.

**Case Report Form:** A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

**Clinical Trial or Study:** Any investigation in human subjects that is intended to discover or verify the clinical, pharmacologic, or other pharmacodynamic effects of an investigational product, to identify any adverse reactions to an investigational product, or to study absorption, distribution, metabolism, and excretion of an investigational product with the object of ascertaining its safety, efficacy, or both. (The terms clinical trial and clinical study are synonymous.)

**Clinical Trial/Study Report:** A written description of a trial or study of any therapeutic, prophylactic, or diagnostic agent conducted in humans, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.

**Contract Research Organization:** A person or organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

**Direct Access:** Permission to examine, analyze, verify, and reproduce any records and reports that are important

in the evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsors, monitors, and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of subjects' identities and sponsors' proprietary information.

**Documentation:** All records, in any form (including but not limited to written, electronic, magnetic, and optical records and scans, roentgenograms, and electrocardiograms) that describe or record the methods, conduct, or results of a trial, the factors affecting a trial, and the actions taken.

**Essential Documents:** Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

**Good Clinical Practice:** A standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected.

**Independent Ethics Committee:** An independent body (institutional, regional, national, or supranational review board or committee), constituted of medical or scientific professionals and nonmedical or nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection by, among other things, reviewing and approving or providing favorable opinion on the trial protocol and the suitability of the investigators, the facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

**Informed Consent:** A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the decision to participate. Informed consent is documented by means of a written, signed, and dated form.

**Investigator's Brochure:** A compilation of clinical and nonclinical data on an investigational product that are relevant to the study of the product in human subjects.

**Monitoring:** Overseeing the progress of a clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and the applicable regulatory requirements.

**Monitoring Report:** A written report from the monitor to the sponsor after each site visit or other trial-related communication, according to the sponsor's standard operating procedures.

**Protocol:** A document that describes the objectives, design, methods, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol-referenced documents. (Throughout the ICH GCP Guideline, the term protocol refers to protocol and protocol amendments.)

**Serious Adverse Event or Serious Adverse Drug Reaction:** Any untoward medical event that occurs in a patient or subject receiving a drug at any dose

and results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

**Source Data:** All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that is necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

**Source Documents:** Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, roentgenograms, and subject files and records kept at the pharmacy, the laboratories, and the medicotechnical departments involved in the clinical trial).

**Sponsor:** An individual, a company, an institution, or an organization that takes responsibility for the initiation, management, or financing of a clinical trial.

**Sponsor-Investigator:** An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

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<sup>a</sup>In this document investigational drugs are defined as those that are being considered for but have not yet received marketing approval by FDA for human use and those that have FDA approval for at least one indication but are being studied for new indications, new routes of administration, or new dosage forms.

<sup>b</sup>The principles and procedures described here are applicable to all clinical drug studies, not just those involving investigational drugs.

<sup>c</sup>In certain emergency situations, prior consent may be waived (21 CFR 50.24).

<sup>d</sup>Definitions selected from reference 5.

*These guidelines were reviewed in 2003 by the Council on Professional Affairs and by the Board of Directors and were found to still be appropriate.*

Approved by the ASHP Board of Directors, November 15, 1997. Developed by the ASHP Council on Professional Affairs. Supersedes the ASHP Guidelines for the Use of Investigational Drugs in Organized Health-Care Settings, dated November 14, 1990.

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The bibliographic citation for this document is as follows: American Society of Health-System Pharmacists. ASHP guidelines on clinical drug research. *Am J Health-Syst Pharm.* 1998; 55:369–76.