Practical Clinical Trials Series

Clinical Research Coordinator Handbook

GCP Tools and Techniques

Second Edition

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This material is presented as an interpretation of the clinical research process based on the expertise and experiences of the authors. therefore not all material will be relevant in every situation. Each situation must be assessed by the appropriate individual and appropriate actions chosen based on individual knowledge, and institutional and sponsor requirements. Every effort has been made to ensure that the contents of this book are factually correct, but the authors and the publisher do not accept liability for injury, damages, or losses arising from material published in this book.

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FOREWORD

The role of the Clinical Research Coordinator (CRC) is central to the successful conduct of a clinical trial. The CRC is involved in every important event in the trial. In fact, many of the investigator's responsibilities are primarily the CRC's operational responsibility, including

- screening patients to ensure rapid, accurate enrollment;
- managing patient scheduling and follow-up;
- informing subjects about the purpose and treatment plan of the study;
- preparing the site for implementation of the treatment plan;
- recording and verifying data in the Case Report Forms;
- keeping study files and records;
- ensuring study supplies are properly inventoried, stored, and reordered as necessary;
- correcting case report problems; and
- transmitting data to the sponsor/CRO.

Investigators, site managers, Clinical Research Associates (CRAs), monitors, and project team leaders from the sponsor and Contract Research Organization (CRO) rely on the skills, knowledge, and abilities of a competent, trained, professional CRC.

The role of the CRC has grown as the clinical research industry has expanded over the past fifteen years. Clinical Research and Development is a relatively young industry, and the role of the CRC is itself relatively new. Fifteen years ago some investigators were still managing their own Case Report Forms, a practice that is still surprisingly common in Europe and Japan. In the late 1980s, the Association of Clinical Research Professionals (ACRP), which today includes the largest CRC membership, was just organizing the CRC Education Committee and beginning to sponsor training programs for CRCs.

In 1990, recognizing that the role of the CRC needed the status of a profession, CRCs in the ACRP began to outline a certification program for CRCs. The work

entailed in certification included important elements of a profession, including identification of job competencies that are important and unique to the professional engaged in the coordination of a clinical research study, development of a job description, and the development of professional standards.

The CRC's evolving role was quickly supported by pharmaceutical companies and CROs, which, in their need for rapid enrollment and clean, quality data, saw the advantages of a professional dedicated to the conduct of the study. Through education and the site selection process, sponsors, CROs, and CRCs together have impressed upon investigators the importance of the skills and knowledge required of a CRC.

Critical to the professionalization of the CRC is the institutionalization of their unique skills, knowledge, and abilities. Unlike most parts of nursing and health care, the CRC is governed not only by professional standards of the healthcare professional but also by a unique set of regulatory requirements, guidelines, and therapeutic area information sheets promulgated by the FDA and in some cases state regulatory agencies. These regulations, often known as the Good Clinical Practices (GCPs), place additional requirements on the CRC not required of other healthcare professionals. That there are, in addition, separate GCPs for the three therapeutic segments of drugs, biological compounds, and medical devices makes the job of the CRC all the more complicated.

Add to that the fact that each sponsor and CRO has its own distinct set of Standard Operating Procedures (SOPs), Case Report Forms, and way of managing the study and the data, including various forms of remote data entry, the job of the CRC becomes quite complicated and challenging; it does indeed contain its own skill set; it is indeed a profession.

In this book, Deborah Rosenbaum, who is both a Certified Clinical Research Coordinator (CCRC) and a Certified Clinical Research Associate (CCRA), and Michelle Dresser, who is a registered nurse with a BSN, have provided an eminently practical description of the responsibilities and functions of the CRC, prefaced by a comprehensive yet succinct guide through the GCP regulations and guidelines. Throughout they provide sample forms, checklists of duties and responsibilities, answers to common questions, and helpful hints, as well as bibliographies that extend the reader's knowledge base. This is a most helpful and practical guide for the CRC.

Frederic Harwood, PhD
Washington, D.C.

PREFACE

Clinical research is a very exciting field—the cutting edge of the future of the practice of medicine. New drugs, new devices, new combinations of drugs, new methods of treatment, and new procedures are explored every day to shape the future of health care. The process of clinical research is also closely regulated by the U.S. Food and Drug Administration (FDA).

As we were working together at Burroughs Wellcome Co. on human immunodeficiency virus (HIV) clinical trials and based on our own experiences as clinical research coordinators (CRCs), we realized a need for a practical reference tool for study coordinators and other research personnel on how to conduct clinical trials. One thing was obvious: most people doing clinical research (clinical research coordinators, investigators, and sometimes monitors) learned the job by on-the-job trial by fire. Although many references and articles about clinical research existed, most were theoretically based and failed to offer practical advice. There were few good references to actually help you GET THE JOB DONE. This completely revised edition of our original 1996 publication provides a logical, step-by-step guide to testing new drugs and treatment modalities in compliance with the latest FDA regulations. This is a hands-on tool for your operation with current forms, International Committee on Harmonisation good clinical practice (ICH GCP) information, FDA regulations, and other references.

The first in a newly revised series aimed at clinical research professionals, this book is written as a reference for what occurs at the study site, in particular, a reference not only for the new study coordinator but also for experienced coordinators. We have provided a regulatory framework with helpful tips on how to accomplish the clinical research process at the site with the regulations in mind. We are sure we have not anticipated every circumstance, but we hope that this book will provide information to solve most problems.

We have also taken into consideration the content of the Association of Clinical Research Professionals (ACRP) CRC certification exam to determine that this book covers all significant parts of clinical research. Although the emphasis in the book might be marginally different from the emphasis of the exam, we feel we have provided information pertinent to the topics selected by the ACRP for the certification process. In addition, in training programs for CRCs, this book has been well received. Many participants found the book to be useful in their day-to-day activities of clinical trial management.

The second book of this series is for the physician investigator, and the third is for the clinical research associate. Each of these books contains information pertinent to these three pivotal roles in the conduct of clinical research. Our goal is that eventually the process of clinical research, as approached by each of these disciplines, will be more consistent and done according to regulation.

We would like to thank Pearl Rosenbaum, Fred Smith, and Susan Poe for their excellent review of the draft manuscript; Jonathon and Georgina Rosenbaum for the artwork in the book; and Laura Weygandt for her assistance with word processing. We'd like to thank our children, Brain Dresser and Sarah and Harrison Rosenbaum, for giving us those "quiet-time" opportunities to write the book and for giving us true pleasure in our lives.

Finally, we'd like to dedicate this book to our mothers, who have taught us so much about life.

Deborah Rosenbaum
Michelle Dresser
August 2001

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OVERVIEW OF CLINICAL RESEARCH

Clinical research is a vital part of health care. Consider where we would be without the medical advances we all take for granted—vaccinations for our children, insulin for diabetics, and pacemakers for people with heart arrhythmias, among others. These developments required years of research by dedicated scientists and clinicians. A recent challenge came with the AIDS (acquired immunodeficiency syndrome) epidemic: a new virus and no effective means of handling it. Although we don't yet have a cure, the scientific community has responded admirably and has developed drugs, therapy plans, and behavior modification programs that, in combination, fight the spread of AIDS. The fight against cancer is another example: In the 1960s, children with acute lymphocytic leukemia had little chance of survival. Now, with sophisticated chemotherapy, many of these children can live to become active, productive adults. Significant strides have been made, but it is clear that there is much clinical research work ahead. The twenty-first century has dawned with a new arena of research—genetic research. With the successful mapping of the human genome, phenomenal implications in the treatment and prevention of diseases are on the horizon and will be our newest research challenge.

The goals of clinical research are to identify the mechanism of the disease process and to determine the effectiveness of intervention in the disease process, generally with drugs, surgery, nutrition, or behavioral changes. In drug research, the specific goals of clinical research include determining the efficacy (effectiveness) and safety of a new drug, as well as defining dose routes and frequencies, testing drug formulations, and exploring combination and adjuvant therapies. This is accomplished through careful planning and implementation of clinical research trials. Additionally, other facets of patient care such as quality of life and pharmacoeconomics have become major topics of research.

Clinical trials are conducted under a very precise plan—the **protocol.** Many other elements of clinical trials, such as the Investigator's Brochure, Case Report Forms, and the investigational agent, accompany the protocol. Because clinical trials involving

investigational new drugs, biologics, or devices are strictly regulated by the U.S. Food and Drug Administration (FDA), specific study documentation must be maintained. The Clinical Research Coordinator (CRC) plays a critical role in putting (and keeping) all of these pieces together.

WHO CONDUCTS CLINICAL RESEARCH?

Clinical research is conducted in a variety of venues. The National Institutes of Health (NIH) sponsor a large number of federally funded trials through the many different institutes. Even within the NIH, rules vary. NCI is very active in consolidating clinical trial information (http://cancertrials.nci.nih.gov). Most prominent is the research that is required by the FDA to provide evidence of safety and efficacy of an investigational product prior to approval for marketing. That is the focus of this manual. However, general research principles apply across the board.

THE DRUG DEVELOPMENT PROCESS

New drugs are developed through a series of laborious steps, as summarized in Table 1.1. New Molecular Entities (NMEs) or New Chemical Entities (NCEs) are novel compounds created in the laboratory by various means from sophisticated computer modeling to happenstance. The compounds are then screened for activity in vitro by established tissue culture screening panels. If activity is noted, the drug is screened for activity in animal models for pharmacology, toxicology, and effectiveness. If the compound appears to have desirable activity and is relatively safe, it will be formulated for clinical trial testing.

Note that these steps are not necessarily sequential but are more likely to be concurrent. For example, while preclinical testing is being conducted in animal models, the formulation of the drug is being designed.

PHASES OF CLINICAL RESEARCH

Clinical research trials are the systematic investigation of the effects of an investigational agent; treatment modality (surgery, radiation); or methods of prevention, detection, or diagnosis of a disease state. Clinical trials are conducted under stringent conditions and specific guidelines outlined in the study protocol.

TABLE 1.1 SUMMARY OF NEW DRUG DEVELOPMENT

Drug Discovery	NMEs discovered by design, happenstance.	
	May be discovered elsewhere and licensed for development.	
Laboratory Screening	Screen NME for activity in specially designed tissue culture screening tests.	
Animal Testing	Screen for activity in specific animal models.	
Preclinical Testing	Toxicology testing (including teratology, carcinogenicity), pharmacology testing, assessment of ADME.	
Formulation Issues	Formulation, stability, and synthesis (small scale and large scale-up for manufacturing).	
File IND Application	Before an investigational agent may be used in humans, an IND (Investigational New Drug) application must be filed with the FDA.	
Clinical Trials	Phase I	"First-time-in-man" studies in normal volunteers.
	Phase II	Efficacy trials in patients.
	Phase III	Large-scale testing in a wider range of patients.
File NDA (New Drug Application)	Data from the clinical trials supporting safety and efficacy are assembled and submitted to the FDA requesting permission to market the compound as a drug for a specific disease.	
Marketing	The drug is marketed for the approved indication.	
Phase IV	Additional trials may be conducted to determine better dosing schedules, new formulations, different populations, and marketing claims.	
Postmarketing Surveillance	After NDA approval, information about the safety of the drug continues to be collected.	

Clinical trials involving the safety and efficacy of NMEs, new formulations, or new indications are generally conducted in phases, as indicated in Table 1.2. It is very important to note that there may be some overlap in development from Phase I to Phase IV. For example, Phase II trials demonstrating efficacy may be completing long-term follow-up while Phase III trials are being initiated, or a drug may be in Phase III testing for one indication and in Phase II for another. Also, it is not always easy to label a clinical trial as a specific phase. These are just general terms used to describe the development of a new drug; some differences in interpretation and overlap may exist.

Also, different types of drugs may have different developmental tracks. "Fast track" drugs typically are reviewed by the FDA prior to extensive Phase III trials. Other studies may not easily fit into a particular phase, for example, a study of a combination therapy of two approved chemotherapeutic agents.

TABLE 1.2 PHASES OF CLINICAL DRUG TRIALS

Phase I: "First-Time-in-Man" Studies

Purpose	Phase I trials are conducted to determine the **SAFETY** of an investigational agent. Pharmacological data are also collected to determine the absorption, distribution, metabolism, and excretion (ADME) of the compound. Generally, initial dosing of the agent is determined from preclinical trials in animals. Most Phase I trials are designed to begin dosing at a subtherapeutic level (to avoid unexpected, catastrophic side effects) with escalating doses to reach the dose-limiting toxicity and determine the maximum tolerated dose (MTD). Pharmacokinetic and pharmacodynamic data are examined in Phase I studies. Data collected from serum levels can be indicative of the effectiveness of the investigational agent in the disease since, typically, predetermined serum levels must be reached to be effective against the disease. Usually, all subjects receive the experimental compound in single or multiple dose. The study is typically conducted by a single investigator at one site.
Length of Studies	Phase I trials are conducted over several months. Individual subject participation may be from one day to several weeks.
Subjects	Generally, normal volunteers without confounding diseases or concurrent medications are recruited to participate in Phase I trials. However, with antineoplastic agents and for certain disease states and to avoid trials in normal subjects, it may be preferred to begin trials in a patient population. For antineoplastic agents, initially trials enroll patients who have failed all other forms of treatment. Although the efficacy of the drug is unknown, it may provide some hope while investigating the side effects of the drug. Phase I trials usually enroll 20–60 subjects.

Phase II: Pilot Trials

Purpose	Phase II trials are conducted to demonstrate **EFFICACY** with a particular disease. These trials are randomized, tightly controlled studies, using small numbers (60–200) of carefully selected patients. When feasible, Phase II trials should be performed comparing a study agent to a placebo or an active control with known efficacy. Subjects may be receiving single or multiple doses. Phase II trials may be conducted at multiple centers.
Length of Studies	Phase II trials may be completed in a few months or take up to several years. Subject participation will vary but is usually of longer duration than in Phase I.
Subjects	Subjects in Phase II trials are patients with the disease or clinical situation being examined. They should be healthy in terms of their disease and free of other serious medical illnesses. These are the subjects you would expect to do well if their disease were managed by conventional means.

Phase IIb: Pivotal Trials

Purpose	Phase IIb trials (sometimes overlap with Phase IIIa) are conducted to gain specific efficacy and safety information for submission of an NDA and are often referred to as *pivotal trials*. Two pivotal trials are typically required to file an NDA with the FDA. Phase II trials also are conducted to determine dose-ranging for Phase III trials.
Length of Studies	Pivotal trials may last a few months to several years. Duration of subject participation depends on the amount of time expected to demonstrate efficacy (reach an endpoint).

Table 1.2 continued on next page

Table 1.2 continued from previous page

Subjects	Subjects are generally patients with the disease without serious complications or other concurrent diseases.

Phase IIIa: Expanded Clinical Trials

Purpose	Phase IIIa trials are designed to gain safety and efficacy information in a large number of patients. Some variables include extended dosing, dose ranging, and patient charactertistics more representative of the market situation. Phase IIIa trials are tightly controlled and are conducted with the experimental agent versus placebo or an active control. Different study designs may be employed. These data are often used to supplement the NDA.
Length of Studies	Phase IIIa studies tend to be of longer duration, lasting one to four years.
Subjects	Phase IIIa subjects are patients exhibiting the disease under study and are selected from a larger population of patients, although entry criteria are still stringent. Several hundred subjects are required in Phase IIIa studies to demonstrate efficacy and assess safety adequately.

Phase IIIb: Large-Scale Trials

Purpose	The purpose of Phase IIIb trials is to gain experience with the experimental agent in a large number of subjects that reflect the general population at risk. Therefore, the trials are less tightly controlled: All subjects may be receiving experimental drug, and entry criteria are relaxed and larger numbers of patients are enrolled. Trials may also be designed to specifically address special patient groups, such as children or the elderly.
Length of Studies	Phase IIIb studies last one to four years and are used to gather additional data about the investigational agent.
Subjects	Phase IIIb trial subjects come from a larger, heterogeneous patient population. The subject population may focus on specific concurrent illnesses to further delineate the drug's safety. This is especially true of geriatric and pediatric patients.

Phase IV: Postmarketing Trials

Purpose	Phase IV trials are done for a variety of reasons: to place the drug in the market ("seeding" studies), to make marketing claims, for pharmacoeconomic studies, for quality of life studies, or for surveillance for unexpected or rare adverse events. New formulations or new indications for a marketed drug must begin with Phase I (new formulation) or Phase II clinical trial designs.
Length of Studies	The length of Phase IV trials is determined by the purpose of the study and may be indefinite, such as in postmarketing surveillance.
Subjects	Subjects in Phase IV trials are drawn from the general population with the specific disease. Further conditions are defined by the purpose of the protocol.

ELEMENTS OF CLINICAL RESEARCH

There are many elements to conducting a clinical trial, and understanding these is critical to the clinical research process. The basic elements are the protocol, the Investigator's Brochure, the investigational agent, data collection forms, and the study files.

Protocol

The study protocol is the blueprint for the study and is required by Good Clinical Practice (GCP) guidelines [21 CFR 312.23(a)]. Generally it includes the following items:

Item	Description
Objective	The "what" of the study. A clear, concise statement of the hypothesis to be tested by the clinical trial. What specific questions is the study designed to answer about the investigational agent at a particular time in its development?
Background and Rationale	The background section of the protocol discusses the known information about the disease and treatment as well as information about the class of drugs being studied. It also summarizes known information about the investigational agent, specifically, side effects known to date. The discussion should lead to the rationale of using the drug(s) in this disease for this study.
Subject Selection Criteria (Inclusion/ Exclusion Criteria)	This section defines the subject population by clearly stating the eligibility criteria for a subject to enroll in the trial.
Treatment Plan	The treatment course (drugs and dosages) is outlined in detail. Additional details describing the study medication include pharmaceutical information (scientific name, chemical structure, stability, appearance, storage requirements), dosage preparation information, packaging information, dose modifications, concomitant medications, dispensing instructions, instructions to patients.
Study Procedures	The "how" of the study. This section includes information on the study design, treatment schedule, tests to be done, time intervals of subject visits and tests, and off-study evaluations.

It also includes information on collecting adverse events, making dose modifications, and handling study dropouts. Many protocols graphically display this information in a table commonly called the study schema or "schedule of study visits and evaluations" (example in Appendix D).

Response Evaluation Criteria

Each protocol must define a priori criteria for patient response to the test agent. These criteria are outlined in detail in this section and discuss objective responses, endpoint variables, measurement of lesions, and so on.

Statistical Section

The statistical section discusses the proposed plan for the evaluation of the data. It includes such items as explanation of study design, feasibility, proposed analyses, conditions under which the study would be stopped, and termination of the study.

Administrative Items

Toward the end of the protocol, requirements for the investigator in conducting the study are discussed. These may include adherence to FDA regulations, monitoring of the trial, data management procedures and completion of Case Report Forms, conditions for early termination of the study, publication policy, or other administrative details.

Bibliography

Lists references cited in the protocol.

Appendices

Some common appendices are as follows:

- Toxicity grading scales.
- Study schema.
- Instructions for evaluating responses.
- Instructions for collecting specific samples.
- Instructions for shipping biological samples.
- Prescribing information (package insert) for active control drugs.
- Sample of patient diary.

- Staging guidelines.
- Quality of Life forms.
- Performance Status Scales (i.e., Karnofsky, Zubrod, ECOG, or WHO).
- Central Radiology Review requirements.
- Gender and Minority Target Accrual.

Investigator's Brochure

The Investigator's Brochure (IB) is a confidential document (sometimes referred to as CIB) provided by the sponsor that summarizes all known information about the investigational drug. This includes preclinical data such as chemical, pharmaceutical, and toxicology data; pharmacokinetic and pharmacodynamic data in animals and in man; and the results of earlier clinical trials. The data should support the use of the investigational agent in the proposed clinical trial and contain information on expected risks or precautions. IBs are updated periodically so that data resulting from clinical trials and further preclinical data can be incorporated. The IB and any revisions should be submitted to the Institutional Review Board (IRB).

Investigational Agent

The investigational agent is the item (drug, device) being studied. It may be an experimental drug, a new combination therapy of approved drugs, or an experimental drug combined with or compared to an approved drug. Also, many experimental agents are studied in conjunction with a placebo control, which also is considered an investigational agent for the trial. In medical device studies, pacemakers, thermometers, contact lenses, and adhesive bandages are all examples of investigational agents when used in a clinical trial of the specific device. STUDY DRUGS ARE NOT SAMPLES. Materials supplied for the study are INVESTIGATIONAL AGENTS and must be stored, dispensed, and monitored as a study requirement (21 CFR 312.57, 312.59, 312.6, and 312.62). More detailed information is included in Chapter 9, "Investigational Agent Management."

Case Report Forms or Data Flow Sheets

Data in clinical trials must be identified and collected in a systematic fashion to assure the data can be analyzed to determine the outcome of the trial (21 CFR 312.62). The Case Report Form (CRF), used by most pharmaceutical sponsors, is used for recording all data pertinent to the study. In some trials, data flow sheets or data summary charts are used to collect data. The CRF or flow sheet should be designed to capture all of the data required by the protocol. The CRF is **completed** by the investigator or the CRC, **reviewed** by the monitor and data management personnel, **entered** into the study database by a data entry specialist, and **analyzed** by statisticians. More detailed information is included in Chapter 7, "Data Management."

Study Files

FDA regulations require that all documents pertinent to the conduct of the clinical trial be maintained (21 CFR 312.62). Items included in the study files are as follows:

Item	Description
Protocol	All versions of the signed protocol and amendments.
Investigator's Brochure	The Investigator's Brochure summarizes all known information about the investigational agent(s).
Form FDA 1572	Statement of Investigator (SOI) (Appendix B). This is the form required for an investigational new drug that the investigator must sign agreeing to adhere to FDA regulations. The form is submitted to the sponsor to submit to the FDA as an amendment to the IND application. Changes in any item on a 1572 will require revisions of this form.
Financial Disclosure	Form FDA 3454 or 3455. Original is submitted to sponsor and a copy is maintained in the study file. The investigator must disclose any financial interest that may bias study results.

Curriculum Vitae (CV)	Current CVs of the investigator and subinvestigators are maintained to establish the qualifications of those conducting the trial.
IRB Approval and Correspondence	Submission letter to IRB, IRB approval letters, reapproval letters, progress reports, and other correspondence as well as the composition (membership list) of the IRB or DHHS (U.S. Department of Health and Human Services) Federal Wide Assurance (FWA) number.
Informed Consent	All IRB–approved versions of the informed consent. Additionally, consent forms signed by subjects must be retained in the study files.
Correspondence	All correspondence between the sponsor and the study site. Any other correspondence relevant to the trial must also be retained.
Telephone Contacts	All records of telephone contacts between the study site and the sponsor (e.g., telephone reports, telephone logs).
Laboratory Certification	The certification of the clinical laboratory by either state or local agencies, the American College of Pathologists (ACP), Clinical Laboratory Improvement Act (CLIA), or other acceptable group. Annual certification must also be retained.
Laboratory Normal Value Ranges	A record of the normal value ranges for all clinical tests used in the clinical trial.
Case Report Forms	A copy of a blank CRF and all completed CRFs (at the end of the study).
Investigational Agent Records	Shipping records (packaging slips) and drug accountability records. At the end of the study, records showing the disposition of the drug (returned to sponsor or destroyed) must be kept on file.

Serious Adverse Event (SAE) Reports	All reports of SERIOUS adverse events. Blank reporting forms should also be supplied in the study file.
IND Safety Reports	Reports of SAEs occurring with the study drug at any study site meeting the FDA definition for reportability.
Study Procedures Manual	A study procedures manual or other instructional information on conducting the study may be provided.
Final Study Report	A copy of the investigator's final report to the IRB (often filed with IRB correspondence). Any publication resulting from the research may be kept in this file.
Monitoring Log	A log of monitoring visits by the sponsor or others is maintained with the study file.
Budget Information	While budget information should be retained, it is recommended that it be kept separate from the study files since this information is not required to be provided to the FDA during an inspection.

Study file records must be retained for

- **two years after FDA approval of the compound for the listed indication, OR**
- **two years after all investigations have been completed and the IND is terminated.**

When applying for approval in global markets, study files must be retained for two years after approval in the last country filed.

THE ROLE OF THE CLINICAL RESEARCH COORDINATOR IN CLINICAL RESEARCH

The primary responsibility of the CRC in clinical research is to ensure smooth, accurate progress of the project from the planning stage through study end (and often beyond) by acting as liaison to the investigator, the subject, the institution, and the company or

government sponsor. Collaboration with individuals possessing the necessary clinical skills and medical expertise for the study will ensure the quality and integrity of a clinical trial.

Qualifications of a Clinical Research Coordinator

Clinical research studies can be fun, exciting, and professionally satisfying, but research isn't for everyone. During the planning phase of clinical trials, it is very important for the investigator to evaluate the coordinator's qualifications for the job and for the candidate to do some self-evaluation.

Ideal Qualifications to Consider

- Scientific/medical background.
- Interest in research methodology.
- Detail oriented.
- Good organizational skills.
- Ability to work independently.
- Innovative and creative.
- Availability per study requirements.
- Flexibility.
- People oriented.
- Good interaction skills with patients.
- Certification in clinical research.

Certification of CRCs

Two organizations currently certify clinical research professionals: the Association of Clinical Research Professionals (ACRP) and the Society of Clinical Research Associates (SoCRA). ACRP certifies both Clinical Research Coordinators (CCRC) and Clinical Research Associates (CCRA) as two separate test processes. Additionally, ACRP is planning for Investigator certification by the end of 2001. SoCRA certifies both CRAs and CRCs but as a single process, and the title is Certified Clinical Research Professional (CCRP). Both certifications require a minimum amount of on-the-job experience plus passing an exam. Contact each organization for additional information.

Responsibilities of Clinical Research Coordinators

Note that the CRC's responsibilities can vary tremendously from institution to institution. The investigator can delegate specific responsibilities to the CRC when appropriate.

Administrative

- Interact with IRB, lab staff, clinic staff, pharmacy, other departments in the institution such as radiology and nursing.
- Assist in preparation of IRB documents including the Informed Consent Document.
- Prepare a study budget.
- Assure all study documentation is maintained.
- Interact with sponsor.
- Interact with Principal Investigator and subinvestigators.
- Coordinate and participate in monitoring visits with sponsor.
- Complete CRFs and submit to sponsor/resolve data queries.
- Facilitate inspections/audits.
- Document study progress.

Coordinator Responsibilities Involving Subjects

- Recruit study subjects.
- Assess subjects for eligibility.
- Discuss study with subject and assist in obtaining informed consent.
- Schedule subject assessments/visits.
- Assure all study tests and visits are done at appropriate time intervals.
- Evaluate study subjects at appropriate intervals.
- Assess laboratory data and clinical signs for potential adverse events.
- Provide information for treatments and reactions.
- Administer or dispense investigational agent as needed under investigator's supervision.
- Promote subject compliance by providing patient support and education.
- Prepare laboratory specimens; shipping biological samples and radiologic films.
- Arrange for study subject compensation.
- Comply with FDA regulations for conducting clinical trials.

THE STUDY WORK AREA

Clinical trials may be conducted in a hospital-based center for either inpatient or outpatient trials, physician's offices or clinics, or special research facilities that concentrate only on clinical research trials.

Too often the work area allocated to the CRC for clinical trial management is inadequate. The following items should be considered when planning a clinical trial:

- Adequate space must be provided for the coordinator to work and store necessary documents.
- If patient exams or interviews are conducted, the room should ensure privacy. If a telephone is necessary, one should be available in the work area.
- Study information is considered *confidential*—files should be locked and CRFs should not be left out where anyone can see them.
- There should be a quiet and private area reserved for the monitor to work in during a monitoring visit (also important for an inspector during an audit).
- Exam rooms should be available for subject visits and equipped with the necessary implements for the study visit.
- If remote data entry is used or if a computer system is used for coordinating the study, adequate equipment and hookups should be available.
- All materials required to conduct the study should be readily available for study assessments.
- The key to a well-run study is *organization*—a tidy office/work area can make all the difference.

RESOURCES

Many resources are available to the CRC; some are listed below. Also, check into educational opportunities offered through your institution, local universities, and regional groups.

Association of Clinical Research Professionals

ACRP is an international organization of individuals involved in clinical research and other research-related professions. It has a large CRC component that is very well organized and active. ACRP offers a certification exam for CRCs. The annual meeting

is held in the spring. ACRP publishes a quarterly newsletter, *The Monitor,* and has previously sponsored the *Journal of Clinical Research and Drug Development.*

> ACRP's mission is to promote the dissemination of information, the exchange of ideas, and the opportunity to network with a wide variety of clinical professionals. In addition to certification, ACRP sponsors an annual meeting attended by 2,000 individuals and 140 exhibitors, a quarterly magazine, an annual directory of members, independents, and service providers, symposia and workshops, a Web page, networking forums, and chapters.

Membership information can be requested as follows:

Association of Clinical Research Professionals
1012 14th Street, N.W., Suite 807
Washington, DC 20005
202-737-8100
202-737-8101 (fax)
www.acrpnet.org

Drug Information Association (DIA)

Mission statement: "To provide a worldwide forum for the exchange and dissemination of information that is intended to advance the discovery, development, evaluation, and use of medicines and related health care technologies." The DIA holds an annual meeting and sponsors topic-specific workshops and seminars. DIA publishes the *Drug Information Journal* and a quarterly newsletter. A membership application form appears in each issue of the journal; information can be requested as follows:

Drug Information Association
501 Office Center Drive, Suite 450
Fort Washington, PA 19034-3211
215-628-2288
215-641-1229 (fax)
dia@diahome.org

Society of Clinical Research Associates (SoCRA)

SoCRA was founded in 1991 to promote professional standards in the management of clinical trials. The group publishes the *SoCRA Source* newsletters. SoCRA offers certification for the clinical research professional (CCRP). Information can be requested as follows:

SoCRA
P.O. Box 101
Furlong, PA 18925
800-SOCRA92 or 215-345-7749
Fax 215-345-7369
www.socra.org

Therapeutic Group Organizations

Groups such as ASCO or ASA often have a CRC component.

Hospital Satellite Network (HSN)

HSN offers information through videotapes and videoconferencing. Often this service is made available through the medical institutions.

National Center for Research Resources (NCRR)

NCRR publishes a bimonthly newsletter, *Reporter*, discussing current research activities. Information can be requested as follows:

Research Resources Information Center
1601 Research Blvd.
Rockville, MD 20850

Center for Clinical Research Practice

Research Practitioner is a bimonthly publication that discusses current issues in clinical research and offers continuing education through self-assessment. The CCRP offers training opportunites. Information can be requested as follows:

Center for Clinical Research Practice
40 Washington Street, Suite 130
Wellesley, MA 02481
781-431-7577
www.ccrp.com

Applied Clinical Trials

Applied Clinical Trials is a journal dedicated to the conduct of clinical trials that is published bimonthly. Information can be requested as follows:

Applied Clinical Trials
859 Willamette Street
Eugene, OR 97401-6806
541-343-1200
541-344-3514 (fax)
www.pharmaportal.com

Patient Information

Taking Part in Clinical Trials is a booklet for patients with cancer [NIH publication number 98-4270 (6/98)]. It is available from

U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health
Cancer Information Service: 800-4-CANCER
www.nci.nih.gov

From Test Tube to Patient: Improving Health Through Human Drugs [FDA Consumer Special Report (9/99)]. This report is available from the FDA and is a great overview of the role of the FDA in the drug approval process. It can be obtained by writing to

U.S. Food and Drug Administration
HFI-40
5600 Fishers Lane
Rockville, MD 20857
888-INFO-FDA
http://www.fda.gov/cder

Protocol Development

FDA Information Sheet, Drug Study Designs
Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials

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Job Descriptions and Performance Evaluations. Carol Saunders, *Research Nurse,* Vol. 5 (6), pp. 1–3, 1999.

Measuring the Workload of Clinical Research Coordinators. Part 1: Tools to Study Workload Issues. Clement K. Gwede, Darlene Johnson, and Andy Trotti, *Applied Clinical Trials,* Vol. 9 (1), p. 40, 2000.

Measuring the Workload of Clinical Research Coordinators. Part 2: Workload Implications for Sites. Clement K. Gwede, Darlene Johnson, and Andy Trotti, *Applied Clinical Trials,* Vol. 9 (2), p. 42, 2000.

New Drugs: First Time in Man. Posnar and Sedman, *Journal of Clinical Pharmacology,* Vol. 29, pp. 961–966, 1989.

The Importance of the Investigator's Brochure. M. Mikhail, *Applied Clinical Trials,* Vol. 2 (6), pp. 56–58, 1993.

The Limitation of Animal Studies: What Can and Cannot Be Predicted for Man. A. D. Dayan, *Drug Information Journal,* Vol. 25, pp. 165–170, 1991.

Who Is a Clinical Research Nurse? Establishing Guidelines and Standards of Practice for a Growing Profession. Karen Bowen and Linda Rice, *Research Nurse,* Vol. 4 (4), pp. 1–4, 1998.

2

FDA REGULATIONS AND GOOD CLINICAL PRACTICE GUIDELINES

Clinical research involving investigational agents in the United States is strictly regulated by the Food and Drug Administration (FDA). Historically, the regulations evolved out of necessity and in response to tragedy (see reference by McCarthy for further information). One ongoing theme in the early attempts at regulation was the inability of the FDA to ENFORCE the regulations—there were no legal means to inspect manufacturers or to bring disciplinary action. Today the FDA has the authority to inspect and bring criminal action against violators of regulatory requirements for the manufacture and sale of food, drugs, and cosmetics.

The regulations specific to the conduct of clinical research in the United States can be found in the *Code of Federal Regulations* (CFR), Title 21, Parts 50, 56, 312, 314, 600, 601 (biologics); and 812, 813, 814 (medical devices); and Title 45, Part 46. Specific topics also may be included in other areas of the CFR. Collectively, these regulations are referred to as Good Clinical Practice (GCP). The regulations for informed consent (21 CFR 50 and 45 CFR 46) and IRBs (21 CFR 56) are aimed at protecting the subjects in clinical trials. Part 312 (IND regulations) enforces this policy in the context of a sponsor's submission of an application to the FDA to begin human trials with an Investigational New Drug (IND). Clinical trial data are collected in support of a New Drug Application (NDA), a formal request to the FDA to approve the investigational new drug for marketing for a specific indication based on data collected from clinical trials. The International Conference on Harmonisation of Good Clinical Practice Guideline offers additional guidance on the conduct of clinical trials. This chapter will focus on the regulations as they apply to investigators, sponsors, the protection of human subjects, and IRBs.

CODE OF FEDERAL REGULATIONS (CFR)

The regulations governing clinical trials are collectively referred to as GCP and are published annually in the CFR. Anyone conducting a clinical trial should take the time to read the regulations. To better understand the regulations, it would be advisable to read the preamble (Part VII) to the IND rewrite of the regulations (*Federal Register,* Vol. 52, Number 53, March 19, 1987, p. 8798). The preamble explains some of the reasoning behind the regulations and provides a context for interpretation.

The relevant parts of the FDA regulations (CFR, Title 21, Parts 50, 56, and 312 and Title 45, Part 46) are included in Appendix A. These are the regulations published in 2000. THE CODE OF FEDERAL REGULATIONS IS UPDATED ANNUALLY, AND IT IS IMPERATIVE THAT AN INVESTIGATOR ALWAYS HAVE A COPY OF THE CURRENT REGULATIONS. The information set forth in this handbook is based on the regulations in effect at the date of publication. **ALWAYS** review the current regulations for changes, and always assess each situation as it applies to your particular case. Verify all processes according to institutional, local, state, and federal regulations. If you do not subscribe to the *Federal Register* or CFR, the university library or the pharmaceutical company sponsor should be able to provide you with current copies. When the sponsor of a clinical trial supplies the investigator with copies of appropriate regulations, verify that they are *current* regulations and not outdated copies. You can access the current regulations at **www.fda.gov**.

Proposed changes to the CFR appear in the *Federal Register,* a document that records government business and is published daily. Generally, comments are invited to a proposed rule by a specified date. The Final Rule, which has considered the comments and has been discussed in a government forum, is then published in the *Federal Register*. When appropriate, the final rule determination is incorporated in the next annual issue of the *Code of Federal Regulations*.

The FDA regulations are supplemented by Information Sheets for investigators, IRBs, and sponsors as well a series of guidelines on the development of specific classes of drugs, based on therapeutic area. The Information Sheets were published in 1989 as a set for the IRB and a set for Clinical Investigators. In October 1995, these Information Sheets were revised and merged into one set, "Information Sheets for Institutional Review Boards and Clinical Investigators." Individual information sheets may be revised as needed. The most current versions may be accessed at www.fda.gov/oc/guidance. Revised again in 1998, the Information Sheets consist of the following:

General

- Frequently Asked Questions.
  - IRB Organization
  - IRB Membership
  - IRB Procedures
  - IRB Records
  - Informed Consent Process
  - Informed Consent Document Content
  - Clinical Investigations
  - General Questions
- Cooperative Research.
- Nonlocal IRB Review.
- Continuing Review After Study Approval.
- Sponsor–Investigator–IRB Interrelationship.
- Acceptance of Foreign Clinical Studies.
- Charging for Investigational Products.
- Recruiting Study Subjects.
- Payment to Research Subjects.
- Screening Tests Prior to Study Enrollment.
- A Guide to Informed Consent Documents.
- Informed Consent and the Clinical Investigator.
- Use of Investigational Products When Subjects Enter a Second Institution.
- Personal Importation of Unapproved Products.
- Exceptions from Informed Consent for Studies Conducted in Emergency Settings.

Drugs and Biologics

- Investigational and "Off-Label" Use of Marketed Drugs and Biologics.
- Emergency Use of an Investigational Drug or Biologic.
- Treatment Use of Investigational Drugs.
- Waiver of IRB Requirements.
- Drug Study Designs.
- Evaluation of Gender Differences.

Medical Devices

- Medical Devices.
- Frequently Asked Questions About IRB Review of Medical Devices.
- Significant Risk and Nonsignificant Risk Medical Device Studies.
- Emergency Use of Unapproved Medical Devices.

FDA Operations

- FDA Institutional Review Board Inspections.
- FDA Clinical Investigator Inspections.
- Clinical Investigator Regulatory Sanctions.

Appendices

- A List of Selected FDA Regulations.
- 21 CFR 50.
- 21 CFR 56.
- Investigations Which May Be Reviewed Through Expedited Review.
- Significant Differences in FDA and HHS Regulations.
- The Belmont Report.
- Declaration of Helsinki.
- A Self-Evaluation Checklist for IRBs.
- FDA District Offices.
- FDA Phone Numbers.
- Internet Sites of Interest for Human Subject Protection Information.

ICH GCP GUIDELINE

The International Conference on Harmonisation (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use was created to standardize technical guidelines and requirements for product registration across the United States, Europe, and Japan to reduce the need for duplication of clinical trials. A listing of ICH Topics appears in Table 2.1, together with Efficacy Guidelines.

TABLE 2.1 ICH TOPICS AND GUIDELINE CATEGORIES

- **Quality** Relating to chemical and pharmaceutical quality assurance
  EX: Q1 Stability Testing
  Q3 Impurity Testing
- **Safety** Relating to in vitro and in vivo preclinical studies
  EX: S1 Carcinogenicity Testing
  S2 Genotoxicity Testing
- **Efficacy** Relating to clinical studies in human subjects
  EX: E3 Structure and Content of Clinical Study Reports
  E4 Dose Responses
- **Multidisciplinary**
  – M1 Medical Terminology
  – M2 Electronic Standards for Transmission of Regulatory Information
  – M3 Timing of Preclinical Studies in Relation to Clinical Trials
  – M4 The Common Technical Document

ICH Efficacy Guidelines

Code	Subject	Number of Guidelines
E1	Exposure	1
E2	Clinical Safety Data Management	3
E3	Study Reports	1
E4	Dose Response Studies	1
E5	Ethnic Factors	1
E6	**Good Clinical Practice**	**1**
E7	Populations	1
E8	Clinical Trial Design	1
E9	Statistical Considerations	1
E10	Choice of Control Group in Clinical Trials	

ICH Guideline E6 is specific to GCP and provides a unified standard for designing, conducting, recording, and reporting trials including human subjects consistent with the Declaration of Helsinki. This Guideline was adopted by the FDA as a guideline effective 9 May 1997. Although the ICH GCP Guideline requires more than the FDA regulations, it does not contradict the regulations.

The ICH GCP Guideline offers distinct and clear concepts to conduct clinical research trials that are a good practice in any clinical research setting. However, it is imperative to comply with ICH GCP Guidelines when the sponsor anticipates submitting a global marketing application to assure that the data will be acceptable to all participating regulatory agencies.

A reference guide to FDA regulations and ICH GCP Guideline E6 by topic is presented in Table 2.2, which also references FDA summary Information Sheets that provide guidelines for investigators, IRBs, and sponsors that have been issued by the Department of Health and Human Services and the FDA. Table 2.3 lists clinical guidelines, by therapeutic grouping, developed by the FDA's Advisory Committees and consultants. These guidelines contain specific information on the conduct of clinical trials. Copies of FDA Information Sheets or clinical guidelines may be obtained by writing to

Food and Drug Administration
FOI Staff
HFI-35, Room 12A-16
5600 Fishers Lane
Rockville, MD 20857
301-443-6310
www.fda.gov/oc/guidance

OR

Executive Secretarial Staff
HFD-8
5600 Fishers Lane
Rockville, MD 20857
301-594-1012
301-594-3302 (fax)

TABLE 2.2 REFERENCE GUIDE TO FDA REGULATIONS AND THE ICH GUIDELINE (E6)

	21 CFR	ICH (E6)	Information Sheets/References*
Abbreviated NDA	314.55	N/A	Organization of an Abbreviated NDA and an Abbreviated Antibiotic Application
Advertising	50.20 and 21 56.111	3.1	Advertising for Study Subjects (9/98) Recruiting Study Subjects (9/98) Payment to Research Subjects (9/98)
Adverse Experiences	310.305	1, 4.11, 5.16, 5.17, 6.8, 7.3.6	
Biologics	600, 601	all	Emergency Use of an Investigational Drug or Biologic (9/98) Investigational and "Off-Label" Use of Marketed Drugs and Biologics (9/98)
Children	50 45 CFR 46 Subpart D	4.8.12	
Compassionate Use IND		N/A	*In* Treatment Use of Investigational Drug (5/89)
Contract Research Organizations	312.52	5.2	

Table 2.2 continued on next page

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	21 CFR	ICH (E6)	Information Sheets/References*
Cooperative Research Review	56.114 45 CFR 46.114	N/A	Cooperative Research (2/89), Nonlocal IRB Review (2/89)
Data Management	312.62		*see* Recordkeeping
Electronic Signature	11		
Emergency Research	50.24		Exception from Informed Consent Requirements for Emergency Research (3/2000)
Emergency Use	312.36	N/A	Emergency Use of an Investigational Drug or Biologic (10/95) Guidance for the Emergency Use of Unapproved Medical Devices (10/22/85)
and Informed Consent	50.23		
Expedited Review	56.110 46 CFR 8980	3.3.5	*Federal Register*, 1/27/91, Vol. 48 (17) Investigations Which May Be Reviewed Through Expedited Review
Federal Policy for the Protection of Human Subjects	46, 50, 56 49 CFR 11, 45 CFR 46 Subparts B, C, D	all	*see* Informed Consent
Fetuses	45 CFR 46 Subpart B	N/A	
Financial Disclosure	54	5.8, 5.9	Forms FDA 3454 and 3455 Finacial Disclosure by Clinical Investigators (3/2001)
Food and Drug Administration			FDA District Offices (10/95), FDA Phone Numbers (10/95) Administrative Practices and Procedures; Good Guideance Practices (10/2000)
Foreign Studies (not under U.S. IND)		N/A	*Federal Register*, Vol. 56 (93) (1991) Acceptance of Foreign Clinical Studies (9/98)
Gender		N/A	Evaluation of Gender Differences (9/98)
Good Clinical Practices	50, 56, 312, 314, 812, 813	all	*Federal Register*, Vol. 52 (53), (3/19/87) Preamble and original Rewrite of regulations, Part VII, p. 8798
Good Laboratory Practices for Nonclinical Laboratory Studies	58		Good Laboratory Practice Regulations: Questions and Answers (6/81) Additional specific guidelines available
Good Manufacturing Practices	211		Specific guidelines available
Information Amendment to IND	312.31	N/A	

Table 2.2 continued on next page

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	21 CFR	ICH (E6)	Information Sheets/References*
Informed Consent	50, 56	1.28, 2.9, 4.8	Informed Consent Regulations
	312.60		Informed Consent and the Clinical Investigator (9/98)
	45 CFR 46		A Guide to Informed Consent Documents (9/98)
Inspections	312.68, 312.58	1.29, 5.19	Compliance Program Guidance Manual (Clinical Investigators)
			Compliance Program Guidance Manual (Sponsors, CROs, Monitors)
			Compliance Program Guidance Manual (IRBs)
			Guide for Detecting Fraud in Bioresearch Monitoring Inspections (4/93)
			FDA Institutional Review Board Inspections (9/98)
			FDA Inspections of Clinical Investigators (9/98)
			Clinical Investigator Regulatory Sanctions (9/98)
IRB and Independent Ethics Committee (IEC)	56	1.27, 1.31, 2	IRB Regulations Institutional Review Board Guidelines
			IRB Compliance Program Guidance Manual
			Sponsor–Clinical Investigator–IRB Interrelationship (9/98)
			Recruiting Study Subjects (9/98)
			Answers to Frequently Asked Questions (9/98)
			Self-Evaluation Checklist for IRBs (9/98)
			Continuing Review (9/98)
			Cooperative Research (9/98)
			FDA Institutional Review Board Inspections (9/98)
			Use of Investigational Products When Subjects Enter a Second Institution (9/98)
			Investigational and "Off-Label" Use of Marketed Drugs and Biologics (9/98)
			IRB Frequently Asked Questions About Review of Medical Devices (9/98)

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	21 CFR	ICH (E6)	Information Sheets/References*
			Payment for Investigational Products (9/98)
			Payment to Research Subjects (9/98)
			Recruiting Study Subjects (9/98)
			Significant Differences in HHS and FDA Regulations for IRBs and Informed Consent (9/98)
			Waiver of IRB Requirements (9/98)
			Cooperative Research (9/98)
			Nonlocal IRB Review (9/98)
			Expedited Review, *Federal Register*, Vol. 48 (17), Jan 1991
			Investigations Which May Be Reviewed Through Expedited Review (9/98)
			FDA Institutional Review Board Inspections (9/98)
Investigator (*see* Obligations of)			
Investigational Agent Management	312.57, 312.59, 312.6, 312.62	1.33, 4.6, 5.11, 5.12, 5.13, 5.14, 7	Preparation of Investigational New Drug Products (draft) (2/88) Charging for Investigational Products (9/98)
Investigational Devices	812, 813, 814	all	*see* Medical Devices
Investigational New Drug Application	312	N/A	Clinical Development Guidelines from the FDA (Table 2.3)
Investigator's Brochure	312.23(a.5)	7	
IND Annual Progress Report	312.33	N/A	
IND Safety Report (Report of Serious Adverse Event)	312.32, 312.64	N/A	Adverse Experience Reporting Requirements for Human Drug and Licensed Biological Products, Proposed Rule, 21 CFR 20, *Federal Register* (10/27/94)
Labeling		N/A	*see* Package Insert
Laboratory Certification	42 CFR 493	8.2.12	
Marketed Drugs		N/A	Investigational Use and "Off-Label" Use of Marketed Products and Biologics (9/98)
Medical Devices	812, 813, 814	all	Emergency Use of Unapproved Medical Devices (9/98)
			Significant and Nonsignificant Risk Device Studies (9/98)
			Medical Devices (9/98)
			IRBs and Medical Devices (9/98)
MEDWATCH Form		N/A	*see* Serious Adverse Experience, IND Safety Report

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	21 CFR	ICH (E6)	Information Sheets/References*
Monitoring	312.53, 312.56	1.38, 5.18	FDA Guideline for Monitoring of Clinical Investigations (1/88)
New Drug Application	314	N/A	Specific guidelines for format and content available from FDA
Obligations of Investigators	312 Subpart D	4	Regulatory Information for Investigators (9/92)
	312.60–312.70		Obligations of Investigators Required Recordkeeping in Clinical Investigations (10/95)
			Informed Consent and the Clinical Investigator (9/98)
			FDA Inspections of Clinical Investigators (9/98)
			Clinical Investigator Regulatory Sanctions (9/98)
			Treatment Use of Investigational Drugs (9/98)
			Drug Study Designs (9/98)
Obligations of Sponsors	312 Subpart D 312.50–312.58	5	Obligations of Sponsors
Package Insert (labeling)	201.57, 314.5(c.2.1)	N/A	
Parallel Track		N/A	*Federal Register*, Vol. 57 (73), (1992), Expanded Access of Investigational Drugs
Postmarketing	314.80	N/A	
Prisoners	50.40 45 CFR 46 Subpart C	N/A	
Product License Application	600, 601	N/A	*refer to* NDA
Protocol	312.23(a.6)	6	Drug Study Designs (9/98)
Protocol Amendment	312.30	6	
Recordkeeping	312.62	2.10, 4.3, 4.9, 5.5, 5.15, 6.13 8.0	Recordkeeping in Clinical Investigations (10/95)
Screening		N/A	Screening Tests Prior to Study Enrollment
Serious Adverse Experience	312.32, 312.64	1.50, 1.60	Adverse Experience Reporting Requirements for Human Drug and Licensed Biological Products, Proposed Rule, 21 CFR 20, *Federal Register* (10/27/94)
			see also IND Safety Report
			MEDWATCH form

Table 2.2 continued on next page

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	21 CFR	ICH (E6)	Information Sheets/References*
Statement of Investigator	312.53	N/A	Form FDA 1572
Subjects	50	1.57	Payment to Research Subjects (9/98)
	45 CFR 46		Recruiting Study Subjects (9/98)
Treatment IND	312.34	N/A	Treatment Use of Investigational Drugs (9/98)
Veterans	41 CFR 16	N/A	
Women	45 CFR 46 Subpart B	N/A	Evaluation of Gender Differences (9/98)

*The FDA and Department of Health and Human Services (DHHS) have issued a series of guidelines or summaries of information to complement the regulations. These Information Sheets are available through Freedom of Information.

TABLE 2.3 GUIDELINES FOR THE CLINICAL EVALUATION OF DRUGS*

- General Considerations for the Clinical Evaluation of Drugs
- General Considerations for the Clinical Evaluation of Drugs in Infants and Children
- General Considerations for the Clinical Evaluation of Analgesic Drugs
- General Considerations for the Clinical Evaluation of Antacid Drugs
- General Considerations for the Clinical Evaluation of Anti-Anginal Drugs
- General Considerations for the Clinical Evaluation of Anti-Anxiety Drugs
- General Considerations for the Clinical Evaluation of Anti-Inflammatory and Anti-Arrhythmic Drugs
- General Considerations for the Clinical Evaluation of Anti-Arrhythmic Drugs
- General Considerations for the Clinical Evaluation of Anticonvulsant Drugs
- General Considerations for the Clinical Evaluation of Antidepressant Drugs
- General Considerations for the Clinical Evaluation of Antidiarrheal Drugs
- General Considerations for the Clinical Evaluation of Antiepileptic Drugs
- General Considerations for the Clinical Evaluation of Antihypertensive Drug
- General Considerations for the Clinical Evaluation of Anti-Infective Drugs
- General Considerations for the Clinical Evaluation of Antineoplastic Drugs
- General Considerations for the Clinical Evaluation of Antiulcer Drugs
- General Considerations for the Clinical Evaluation of Bronchodilator Drugs
- General Considerations for the Clinical Evaluation of Drugs for the Treatment of Congestive Heart Failure
- General Considerations for the Clinical Evaluation of Drugs to Prevent, Control and/or Treat Periodontal Disease
- General Considerations for the Clinical Evaluation of Drugs to Prevent Dental Caries
- General Considerations for the Clinical Evaluation of Drugs Used in the Treatment of Osteoporosis
- General Considerations for the Clinical Evaluation of Gastric Secretory Depressant Drugs
- General Considerations for the Clinical Evaluation of General Anesthetics
- General Considerations for the Clinical Evaluation of G.I. Motility-Modifying Drugs
- General Considerations for the Clinical Evaluation of Hypnotic Drugs
- General Considerations for the Clinical Evaluation of Laxative Drugs
- * General Considerations for the Clinical Evaluation of Lipid-Altering Agents
- General Considerations for the Clinical Evaluation of Local Anesthetics
- General Considerations for the Clinical Evaluation of Nonsteroidal Anti-Inflammatory and Anti-Rheumatic Drugs
- General Considerations for the Clinical Evaluation of Psychoactive Drugs in Children
- General Considerations for the Clinical Evaluation of Radiopharmaceutical Drugs
- Guidelines for Abuse Liability Assessment
- Guidelines for the Evaluation of Controlled Release Drug Products
- Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs
- Guidelines for the Study of Drugs Likely to Be Used in the Elderly

*Guidelines are available from the FDA through Freedom of Information. Additional guidelines can be obtained at www.fda.gov/cder/guidance/index.htm or www.fda.gov/foi/foia2.htm.

RESPONSIBILITIES OF INVESTIGATORS

In signing the **Statement of Investigator form (Form FDA 1572),** the investigator agrees to ensure that an investigation is conducted according to the provisions in the statement of investigator, the investigational plan (protocol), and applicable regulations. Specifically (adapted from Form FDA 1572 and 21 CFR 312.60–312.70):

Protocol	Conduct the study according to the current protocol and make changes only after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
Study Conduct	The investigator will PERSONALLY conduct or supervise the investigation.
Informed Consent and IRB Requirements	Inform subjects that the study is investigational and assure that informed consent regulations (21 CFR 50) and IRB regulations for review and approval (21 CFR 56) are met.
Adverse Experiences	Agrees to report adverse experiences to the sponsor in accordance with 21 CFR 312.64 (see Chapter 8).
Investigator's Brochure	The investigator must read and understand the information in the investigator's brochure, especially the potential risks and side effects.
Inform Investigative Staff	The investigator agrees to ensure that all associates, colleagues, and employees assisting in the conduct of the trial are informed about their obligations in meeting these commitments.
Subject Records	The investigator will maintain adequate and accurate records (21 CFR 312.62) and make the records available for inspection (21 CFR 312.68). Case histories shall be prepared and maintained to record all observations and other pertinent data for each individual treated (21 CFR 312.62).

IRB

The IRB must be in compliance with 21 CFR Part 56. The investigator will be responsible for obtaining the initial and continuing review and approval of the study. He/she must report to the IRB all changes in the research activity and unexpected risks to subjects or others. He/she will not make any changes in the research plan without IRB approval, except when necessary to protect subjects (21 CFR 312.66).

Regulations

The investigator agrees to comply with pertinent requirements in 21 CFR 312.

Investigational Drug

The investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. He/she shall not supply investigational drug to any person not authorized to receive it (21 CFR 312.61). The investigator is required to maintain adequate records of the disposition of the investigational drug, including dates, quantity, and use by subjects. Unused supplies shall be returned to the sponsor or otherwise properly disposed (alternative disposition, 21 CFR 312.59) if the study is completed, terminated, discontinued, or suspended (21 CFR 312.62).

Record Retention

The investigator must maintain records (study files) for the study for a period of two years following the date of NDA approval for marketing for the indication being studied; or, if no application is filed or is not approved, until two years after the notification to the FDA that the investigation (IND) is discontinued (21 CFR 312.62).

Investigator Reports

The investigator is responsible for progress reports to the IRB, safety reports of unexpected serious adverse events (IND safety reports), and the final report summarizing the study (21 CFR 312.64).

Inspections The investigator will permit the FDA to have access to, copy, and verify any records or reports made by the investigator. The investigator is not required to divulge subject names unless more detailed study of the cases is required or there is reason to believe that the records are not representative of actual cases or results (21 CFR 312.68).

Controlled Substances For drugs subject to the Controlled Substances Act, the investigator shall take adequate measures to prevent theft or diversion into illegal channels of distribution (21 CFR 312.69).

Disqualification Investigators may be disqualified for failure to comply with regulations (21 CFR 312 Subpart D, Part 50, and Part 56) or submitting false information to the sponsor (21 CFR 312.70). The process of disqualification is outlined in Part 312.70.

RESPONSIBILITIES OF THE SPONSOR

The sponsor also has specific obligations as outlined in the FDA regulations, one of which is to monitor the investigator to assure that he/she is adhering to his/her obligations. But remember, the sponsor has a lot at stake here—the future of the investigational agent. Because of this, the sponsor does not want to risk the disqualification of an investigator or have any unfavorable attention from the FDA. Therefore, the sponsor will be very insistent that the investigator conduct the study as written and according to GCP.

In addition to specific regulations regarding the conduct of clinical trials, sponsors also must adhere to regulations pertaining to the IND Application (21 CFR 312), an NDA (21 CFR 314), Good Manufacturing Practices (21 CFR 211), and Good Laboratory Practices (21 CFR 58).

The general responsibilities of the sponsor, as outlined in 21 CFR 312.50 are as follows:

- To select qualified investigators.
- To provide investigators with information needed to conduct the investigation properly.

- To ensure proper monitoring of investigations.
- To ensure the investigation is conducted according to the general investigational plan and protocols contained in the IND.
- To maintain an effective IND.
- To ensure that the FDA and investigators are promptly informed of significant new adverse events or risks.

The specific responsibilities of the sponsor (adapted from 21 CFR 312.53–312.59) are as follows:

Selecting Investigators

Investigators must be qualified by training and experience as experts to investigate the drug [21 CFR 312.53(a)].

Investigational Agent

Investigators receiving the drug must be registered with the FDA (via a Statement of Investigator form) to receive this investigational drug under this IND (21 CFR 312.53). The investigator must keep records (shipping papers, accountability logs, destruction records) to show disposition of the investigational drug (21 CFR 312.57). The sponsor shall keep in reserve any sample of a test article used in bioequivalence or bioavailability study (21 CFR 312.57). The sponsor shall assure that adequate precautions are taken to prevent theft or diversion of a controlled substance to illegal channels (21 CFR 312.58). The sponsor shall assure the return of all unused supplies of the investigational agent from investigators whose participation is discontinued or terminated (21 CFR 312.59) or may authorize alternative disposition of unused drug (21 CFR 312.59).

Investigators

Before an investigator may begin using the investigational agent in the study, the following information must be obtained by the sponsor (21 CFR 312.53):

- Completed Statement of Investigator (Form FDA 1572).
- Curriculum Vitae.
- Protocol (authored by either the investigator or sponsor) and CRFs.

The sponsor shall keep the investigator informed by providing an investigator's brochure before the study begins (21 CFR 312.55). The sponsor shall keep the investigator informed of any new observations regarding adverse effects and safe use of the investigational drug and relay any important safety information resulting in an IND Safety Report to the investigator (21 CFR 312.55).

Monitoring

The sponsor must select monitors who are qualified by training and experience to monitor the progress of the investigation (21 CFR 312.53). The sponsor shall monitor the progress of all clinical investigations being conducted under the IND (21 CFR 312.56).

Investigator Compliance

If a sponsor discovers that an investigator is not complying with the signed Statement of Investigator, the investigational plan, GCPs, or other requirements, the sponsor must either secure compliance or discontinue shipment of investigational drug and end the investigator's participation in the study (21 CFR 312.56 and 312.70).

Safety

The sponsor shall review and evaluate the data relating to safety and efficacy as it is obtained from the investigator to be reported to the FDA as IND Annual Progress Reports (21 CFR 312.33) or IND Safety Reports (21 CFR 312.32 and 312.56).

If the sponsor should determine that the investigational drug presents an unreasonable and significant risk to subjects, the sponsor shall discontinue those investigations, notify the FDA, notify all investigators and IRBs, assure disposition of the investigational agent, and provide the FDA with a full report. Investigations must be terminated no later than 5 days after the decision to discontinue is made (21 CFR 312.56).

IND Safety Reporting Requirements

According to 21 CFR 312.32, sponsors shall promptly review all information relevant to the safety of the drug. The sponsor must notify the FDA in a written report of any serious and unexpected adverse experience associated with the use of the drug within fifteen days after the sponsor's initial receipt of the information. The FDA must be notified by telephone of any unexpected fatal or life-threatening experience associated with the use of the investigational agent no later than seven days after receipt of the information (21 CFR 312.32). The sponsor must relay all important safety data to all investigators in a timely manner (21 CFR 312.55). IND safety reports are discussed in greater detail in Chapter 8.

Recordkeeping and Record Retention

The sponsor must maintain adequate records of investigational agent receipt, use, and other disposition (21 CFR 312.57). The sponsor shall maintain required records of the study conduct for two years after NDA approval or until two years after notification to the FDA that shipment and delivery of the drug for investigational use has been discontinued (21 CFR 312.57).

Inspections

The sponsor shall permit FDA to have access to, copy, and verify any records and reports relating to the investigation (21 CFR 312.58). The sponsor shall discontinue shipment of drug to any investigator who has failed to maintain or make available records or reports as required (21 CFR 312.58).

IND Annual Progress Reports

The sponsor must submit a brief report of the progress of studies under the IND annually. Generally, the reports include a summary of studies, summary information on all clinical data (for example, IND safety reports, tabulation of adverse experiences, dose response data), and preclinical data. Specific requirements for the content are included in 21 CFR 312.33.

Additional specific regulations apply to the sponsor and are detailed in Part 312.

The sponsor may transfer certain obligations to a Contract Research Organization (CRO). In this case, the CRO is responsible for the obligations of the sponsor as specified in a written agreement (21 CFR 312.52). They, in effect, become the "sponsor."

FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS

The financial disclosure regulation (21 CFR 54) was established for the FDA to address payment arrangements and financial interests of investigators that could potentially bias the outcome of the study. Sponsors must submit information concerning compensation to, and financial interests of, any clinical investigator conducting clinical trials where the FDA relies on the data to support efficacy, safety, or bioequivalency to ensure that the reliability of the data is not affected.

The financial interests of investigators, subinvestigators, and their spouses and dependent children must be disclosed if the amount meets the criteria of 21 CFR 54. This includes

- a situation where the value of compensation for the study could affect the study outcome (i.e., compensation for a favorable outcome is higher);
- proprietary interest in the investigational agent (patent, licensing agreement, or trademark);
- equity interest in the sponsor company (greater than $50,000); and
- any other significant payment by sponsor, i.e., royalties (greater than $25,000).

The sponsor must obtain Certification of Financial Disclosure from the investigator conducting the clinical trial using one of two FDA forms:

- Form FDA 3454: Certification of absence of financial interest
- Form FDA 3455: Disclosure statement which reveals the presence of financial interests

When there is a significant financial interest for the investigator, the sponsor must take steps to minimize bias by that investigator.

The sponsor submits a list of all investigators (principal and subinvestigators) to the FDA and appropriate Forms 3454 and 3455. If the sponsor does not submit these records with the marketing application, the FDA may refuse to file the application.

The FDA has published a Guidance for Industry, Financial Disclosure by Clinical Investigators, effective March 20, 2001.

ELECTRONIC SIGNATURE (21 CFR 11)

The regulations pertaining to electronic signatures provide the FDA's criteria for acceptance of electronic records and signatures to ensure data integrity and validity. An electronic document is "any combination of text, graphics, data, audio, pictorial, or other information in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system." Electronic signatures document that a file and its contents were produced or audited by a particular, authorized individual. Instead of a graphic image of a signature, the electronic signature can be a computer code, i.e., unique identification code and password, that only the originator can use. The signature code should provide identification and verification of the originator by two separate means and also create an audit trail.

The regulation requires that there are technical and procedural controls within the system to assure data integrity by using validation systems. The system must be capable of producing paper copies. The computerized system must also be maintained as systems change or have adequate and accurate means of upgrading to the newer system.

THE INSTITUTIONAL REVIEW BOARD

The IRB is responsible for reviewing clinical investigations with the intent to protect the rights and welfare of human subjects involved in such investigations. FDA regulations specific to IRBs are in 21 CFR 56. An IRB "means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects" [21 CFR 56.102(g)]. The IRB is a generic term used to describe the committee that is responsible for review of research and protection of rights and welfare of research subjects. An institution may choose any name for this board.

Functions and Operations

IRB functions and operations are outlined in 21 CFR 56.108, as below. (Note: IRBs must establish and follow WRITTEN procedures to fulfill these functions and operations.)

- Conduct initial and continuing review of research and report its findings and actions to the investigator and the institution.

- Determine which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred during the review period.
- Ensure prompt reporting to the IRB of changes in research activity.
- Ensure that changes to approved research plans may not be implemented without IRB review and approval except when necessary to remove immediate significant hazard to protect subject safety.
- Ensure prompt reporting to the IRB, institutional officials, and the FDA of any unanticipated risks to subjects, any instance of serious or continuing non-compliance with these regulations, and any suspension or termination of IRB approval.
- Review proposed research at convened meetings where a majority of IRB members are present including one member whose primary interests are in nonscientific areas (see membership).
- Approval by a majority of those members present is required for the research to be approved.

IRB Membership

The membership composition of IRBs is very carefully selected. According to FDA regulation (21 CFR 56.107):

- IRBs must have at least five members with varying backgrounds, qualified through experience and expertise, diversity (consideration of gender, race, cultural backgrounds), and sensitivity to community attitudes.
- Every nondiscriminatory effort should be made to ensure that an IRB does not consist entirely of all men or all women.
- Each IRB should have one member whose primary concerns are scientific and one member whose are nonscientific.
- Each IRB shall include a member who is not personally affiliated with the institution and does not have an immediate relative affiliated with the institution.
- An IRB member may not participate in the review of any research where the member may have a conflicting interest, although he/she may provide information to the IRB as requested. Such conflicts would include reviewing studies where the member is on the investigative staff for the study, reviewing studies funded

by sponsors who contribute to the member's research, or reviewing studies of sponsors in which the member has a financial stake (e.g., stock in the company) [21 CFR 56.107(e)].

- An IRB may invite experts to assist in the review of complex issues, but these individuals may not participate in IRB voting.

One member may satisfy several membership requirements, for instance, one female or one male in a nonscientific field not affiliated with the institution.

Review of Research

The purpose of IRB review of research is to assure that the research is sound and that the subjects are being treated fairly and safely. Some areas that the IRB will consider during the review process are as follows:

Subjects

- Are risks to subjects minimized and reasonable?
- Procedures should be consistent with sound research design and should not unnecessarily expose subjects to risk.
- Whenever possible, procedures are those that would ordinarily be performed on patients for diagnostic or treatment purposes according to standard of care regardless of study participation.
- The potential benefit of the treatment to the subject should be reasonable in relation to the risk.
- Selection of subjects must be fair and equitable.
- Informed consent will be obtained for each prospective subject as required in 21 CFR 50.
- Subjects will be adequately monitored for safety as outlined in the research plan (protocol).
- Provisions are taken to adequately protect the subject's privacy and maintain confidentiality of the data.
- Study procedures do not put subjects at risk, for example, the amount of blood collected at one visit or over a period of time is not so excessive as to put the subject's health at risk.

Study Design

- The study is designed appropriately to obtain and collect results.
- Testing parameters are reasonable.
- Study visits are not too frequent, but subject contact is adequate to assess safety.
- Provisions for handling adverse events (dose reductions, unblinding, specific treatment plans) or subjects who fail to respond are clearly outlined.
- There is sound scientific reasoning to support the study plan.

Investigator

- The investigator is qualified by experience and education to conduct the trial.
- Often the investigator has a "track record" at the institution so that the IRB is aware of his/her capabilities.

According to 21 CFR 56.109, the IRB shall

- Review and approve, require modification to (for approval), or disapprove research activities that are subject to FDA regulation.
- Require that information be given to subjects for obtaining informed consent as outlined in 21 CFR 50.25. The IRB will determine if that information (Informed Consent Form, video presentation, short form, etc.) is adequate and may require modifications.
- Require documentation of informed consent (21 CFR 50.27). The IRB may waive this requirement if the research presents no more than minimal risk of harm to study subjects and involves no procedures that normally require written consent outside the research context. In these situations, the IRB may require that a written summary of the research be provided to the subject.
- Notify investigators and the institution in writing of its decision to approve or disapprove a research proposal. Disapproval letters should include the reason(s) for the decision. The investigator has the opportunity to respond in writing.
- Conduct continuing review of the research at least annually but more often according to the degree of risk to subjects.
- Have the authority to observe the consent process and the research or appoint a third party to do so.

Special Circumstances

Sometimes there are special circumstances that affect the review of research by the IRB:

Expedited Review

Research involving no more than minimal risk or minor changes (amendments to protocols) to approved research may be reviewed and approved without a full IRB meeting (21 CFR 56.110). Specific categories are published in a list in the *Federal Register* (November 9, 1998), 21 CFR 56.110. Generally, the IRB chairperson or designated member(s) will carry out the review process. Expedited review is subject to all authorities of the IRB except that research may not be disapproved. A full committee must be convened to disapprove research. IRBs must establish a method to keep all members informed of expedited review activities.

Emergency Research

When research involves subjects who are unable to consent because of the emergency situation, such as heart attack, stroke, or motor vehicle accident, but the investigational agent or procedure is important to be studied and may benefit the patient and there are no other subject populations to answer the research question, then a sponsor may conduct the research under Emergency Research guidelines. Emergency Research is addressed in 21 CFR 50.24 but also applies to Parts 56 and 312. An Information Sheet, "Exception from Informed Consent Requirements for Emergency Research (3/31/2000)," clarifies some of the requirements.

Emergency Use

In certain situations, such as medical emergencies or life-threatening situations, the regulations provide for IRB review and approval for the emergency use of nonapproved drugs. In an emergency situation where there is no time for the review and approval process, the physician may treat with an investigational agent, but then must submit the following to

the IRB within five working days of the emergency use of an unapproved treatment:

- Name of subject.
- Name of investigational agent.
- Statement of rationale for use of the investigational treatment.
- Copy of the signed Informed Consent Form or a statement from the investigator and a statement from a physician not involved with the clinical investigation verifying that the situation was life-threatening, necessitating the use of the agent, informed consent could not be obtained, and no alternative method of approved or generally accepted therapy was available for this subject.
- Approvals for emergency situations are on an individual basis, and each situation must be presented to the IRB.

Compassionate IND ("single patient use")

In a situation where a patient has failed all available treatments or there is no approved treatment available, but there is some evidence that a proposed treatment may be beneficial based on theoretical grounds, the FDA may permit the use of the proposed treatment under the sponsor's IND or under a new IND filed by the investigator for an identified patient. All outcome data must be reported to the FDA. These instances may be treated as pilot studies, and if the data look promising, controlled clinical trials should be pursued. See the FDA Information Sheet "Treatment Use of Investigational Drugs" (9/98).

Treatment INDs

A current trend allowing new drugs to get to patients more quickly is to offer the drug (usually while the NDA is pending at the FDA) through a treatment IND. Treatment INDs may be submitted for individual patients, or as a package to treat all qualified patients based on a substantial amount of evidence available on the drug's safety and effectiveness. Prospective

IRB approval (including an Informed Consent Form) is required [21 CFR 312.34 and FDA Information Sheet "Treatment Use of Investigational Drugs" (9/98)].

Marketed Drugs

Research involving marketed drugs also requires IRB approval. A full protocol or study plan must be prepared and submitted to the IRB. [See the FDA Information Sheet "Investigational Use and 'Off-Label' Use of Marketed Products, Biologics, and Medical Devices" (9/98).]

Medical Devices

Regulations for IRB approval apply to the investigational use of medical devices. (Pacemakers, IUDs, bandages, thermometers, intraocular lenses, in vitro diagnostic products are a few examples.) Further information is available from the FDA Information Sheet "Frequently Asked Questions About IRB Review of Medical Devices" (9/98).

Cooperative Research

Institutions involved in multi-institutional studies may use joint review, review by another qualified IRB, or similar arrangements to avoid duplication of effort. However, at some institutions, the IRB may still request local review for studies conducted at the institution. If there is a local IRB, notify the board of the study and approval by a separate IRB. Submittal of approval documents from other institutions may facilitate the local review (21 CFR 56.114 and 45 CFR 46.114). Refer to Information Sheet "Cooperative Research" (9/98).

Private Practice

Research conducted in a private practice setting must have IRB review and approval. Generally, the investigator may use the IRB at the institution where he/she has admitting privileges, use an established IRB at a local institution, establish an IRB, or hire an independent IRB.

The Approval Letter

The IRB approval letter should contain the following information:

- Name and address of the IRB.
- Date of approval.
- Investigator name.
- Title of the study.
- Statement that the research protocol and informed consent have been approved.
- List of any other materials reviewed, e.g., advertisements.
- Comment regarding updates, reapproval date.
- Signature of the IRB chairperson or appointed representative.

Ongoing Review

The IRB must conduct continuing review of the research at least annually and more frequently if the IRB determines it to be indicated by the degree of risk involved with the study.

Suspension of Research

In accordance with 21 CFR 56.113, the IRB has the authority to suspend or terminate approval of research that is not being conducted in compliance with the IRB's requirements or that has been associated with unexpected serious risk to subjects. Suspensions and terminations must be reported with a statement of the reason(s) for the IRB's action to the investigator, institution officials, and the FDA.

Studies Exempt from IRB Approval

Certain types of studies are exempt from the IRB review and approval process, as defined in 45 CFR 46.101(b). However, it may be necessary to submit a study application to the IRB to ascertain that these conditions are met. Exempt studies may include the following:

- Research involving normal educational practices.
- Research involving the use of educational tests, survey procedures, interview procedures, or observation of public behavior.

- Research involving the review of existing data, documents, records, or specimens, if these sources are publicly available or if subjects cannot be identified, directly or through identifiers linked to the subjects.
- Research and demonstration projects designed to evaluate public benefit or service programs.
- Research involving taste and food quality evaluation and consumer acceptance [21 CFR 56.104(d)].

In any of these situations, refer to specific regulations and submit the information to the IRB according to the institution's policy and governing regulations.

Advertising

IRBs are responsible for reviewing the methods of recruiting study subjects to assure equitable selection of subjects [21 CFR 56.111(a)(3)]. One method used by investigators is advertising. IRBs review the information contained in the advertisement and the medium used (newspaper, TV, poster, leaflet, etc.) to determine that the rights and welfare of subjects are protected. Advertisements used to recruit subjects should comply with the regulations governing informed consent and subject selection processes [21 CFR 50.20, 50.25, and 56.111(a)(3)].

IRBs should assure that information in advertisements avoids undue coercion and is not misleading to subjects. This is especially relevant to subjects with acute or severe physical or mental disabilities or subjects who are economically or educationally disadvantaged who may need extra protection to assure their rights [21 CFR 56.111(b)].

Generally, advertisement should be limited to

- the name and address of clinical investigator or institution,
- the purpose of the research and summary of eligibility criteria,
- a description of recruitment incentives to subject (payments or free exams),
- time commitment required of participants,
- the location of the research, and
- whom to contact for further information.

No claims of effectiveness, safety, or superiority to other drugs should be made or implied. Such information would be misleading to subjects and also a violation of FDA regulations involving promotion of investigational agents [21 CFR 312.7(a) and 812.7(d)].

When recruiting from other physicians, nurses, and so on, it is *not* recommended to offer a referral fee. However, you may offer to forward the subject's pertinent study data

or arrange for the subject to be seen for study visits (with reimbursement) at the local physician's office (in which case you may need to include the physician as a subinvestigator on Form FDA 1572 and arrange for reimbursement).

Advertising for study subjects may be submitted to the IRB with the initial protocol or at a later date but must receive approval of the IRB prior to implementation.

IRB Records and Reports

The IRB is required to maintain documentation of IRB activities, such as the following:

- Copies of all research proposals, sample informed consent documents, investigator's progress reports, and reports of injuries to subjects.
- Minutes of IRB meetings.
- Records of continuing review activities.
- Copies of all correspondence between the IRB and investigators.
- Detailed list of IRB members.
- Written operating procedures [21 CFR 56.108(a) and (b)].
- Statement of significant new findings provided to subjects (21 CFR 50.25).

The records shall be retained for at least three years after study completion. Records must be made available for inspection and copying by FDA representatives (21 CFR 56 Subpart D).

Sponsors and IRBs

Sponsors must assure that IRBs are operating in compliance with 21 CFR 56 and 50 (informed consent regulations). This is usually accomplished without direct interaction between the IRB and the sponsor.

- Documents of correspondence between the investigator and the IRB are kept in the study file and will be checked by the monitor (and by an inspector during an audit).
- The informed consent document will be reviewed by the sponsor prior to study initiation. During the trial, the monitor will ensure that each subject has signed a valid consent form.
- The sponsor will usually request a list of IRB membership to ascertain that membership meets FDA requirements. Additionally, or alternatively, the sponsor

may request the DHHS "general assurance" or Federal Wide Assurance (FWA) number or some other statement that the IRB conforms to 21 CFR 56.

This does not imply that the sponsor is responsible for the detailed compliance of IRBs. The sponsor must rely on the clinical investigator to assure that the IRB is in compliance, especially when the investigator and IRB are in the same institution. When an independent IRB is used, it would be wise for both the sponsor and investigator to carefully inspect the IRB for compliance to FDA regulations. Results of FDA IRB inspections (Establishment Inspection Reports or EIRs) may be obtained through the Freedom of Information process.

Inspection of IRBs

The FDA Bioresearch Monitoring Program includes a provision for the inspection of IRBs to ensure the protection of human subjects through well-organized and properly functioning IRBs. The FDA conducts on-site procedural reviews of the IRB to determine whether an IRB is operating in accordance with its own written procedures as well as in compliance with current FDA regulations. See the FDA guideline "FDA Institutional Review Board Inspections" (9/98) for further information. Administrative actions for noncompliance are included in 21 CFR 56 Subpart E.

The Office for Human Research Protections (OHRP) protects humans participating in biomedical and behavioral research under the DHHS, which includes both the National Institutes of Health (NIH) and the FDA. OHRP replaced the Office for Protection from Research Risks (OPRR) in June 2000. OPRR previously only had oversight over research sponsored by the NIH. OHRP has the authority to suspend research at institutions where there are violations of human subject rights regardless of sponsorship.

SUBJECT INFORMED CONSENT

The protection of the rights and the welfare of research subjects is an important aspect of the regulations. Protection of human subject rights and safety is specifically addressed in 21 CFR 50. Additional regulations under the DHHS are found in 45 CFR 46. To gain an appreciation for the intent of the regulations, it is recommended to review the Declaration of Helsinki (see Appendix C) and the Belmont Report.

Anyone involved in a research trial has a right to know what that involvement entails. To assure that research subjects are given this crucial information, the regulations require

that the research subject give "informed consent" to participate in a research trial. This is most commonly accomplished by preparing an Informed Consent Form. After discussion with the subject, the subject will sign the form signifying agreement to participate in the study and documenting his/her understanding of the risks and benefits.

It is important to remember that getting the subject to sign the Informed Consent Form does not, in and of itself, constitute informed consent. The consent form is an aid to assure that the subject is receiving adequate, consistent information about participating in the research trial. Signing the form provides documentation of the subject's consent to participate in the study. The "Obtaining Informed Consent" section in Chapter 6 suggests techniques to use when obtaining informed consent from research subjects.

A consent form should be prepared for each research trial and be specific to the protocol. *General requirements* for informed consent are contained in 21 CFR 50.20, and include the following:

- No investigator may involve a human being as a research subject unless the investigator has obtained legally effective informed consent from the subject or the subject's legally authorized representative (except as provided in Part 50.23).
- The prospective subject or representative must have sufficient opportunity to consider the study with minimal possibility of coercion or undue influence.
- The information presented to the subject must be in a language understandable to the subject.
- The informed consent shall not include exculpatory language through which the subject may waive his/her legal rights or that releases the investigator, sponsor, or institution from liability for negligence.

EXCEPTION from the general requirements (Part 50.23; all conditions must be met and verified in writing both by the investigator and a physician not involved in the research) would require that:

- the subject is confronted with a life-threatening situation necessitating the use of the investigational agent,
- informed consent cannot be obtained because of an inability to effectively communicate with the subject,
- consent cannot be obtained from the subject's legal representative in a timely manner, and

- there is no alternative treatment available that provides an equal or greater likelihood of saving the life of the subject.

If time is not sufficient to obtain independent determination by a noninvolved physician, the determinations of the investigator shall be made and reviewed and evaluated by a physician not participating in the study within five working days of use of the investigational agent.

All documentation must be submitted to the IRB within five working days after the use of the investigational agent.

Certain exceptions may apply to the use of investigational agents under an IND sponsored by the Department of Defense. These are summarized in Part 50.23(d).

Emergency Research situations may also include exceptions from pretreatment informed consent (21 CFR 50.24). Review the FDA Information Sheet "Exception from Informed Consent Requirements in Emergency Research: Regulatory Language and Excerpts from Preamble" (3/2000).

Elements of informed consent are addressed in Part 50.25. Table 2.4 summarizes the basic elements and additional elements of informed consent.

Documentation of Informed Consent

Informed consent must be documented by the use of a written form approved by the IRB except where minimal risk [as defined in 56.109(c)] is involved. The subject or the subject's legal representative must sign the form. A copy is given to the person signing the form. The consent form may be either a

- written document including all of the elements of informed consent (21 CFR 50.25, Table 2.4) or
- short form stating that the elements have been orally presented to the subject or the subject's legal representative. A witness is required for the oral presentation. Also, a written summary of what is to be presented to the subject must be approved by the IRB. The subject or his/her representative must sign the short form. The witness must sign both the short form and a copy of the summary. The person presenting the consent must sign a copy of the summary. A copy of the summary is given to the subject or his/her representative (21 CFR 50.27).

TABLE 2.4 INFORMED CONSENT CHECKLIST

There are eight REQUIRED ELEMENTS of informed consent. These elements MUST be present in the Informed Consent Form or the summary for the short form:

1. The Informed Consent Form must CLEARLY state that the study involves RESEARCH.
   - State the study purpose in terms that the subject can understand.
   - Identify all experimental drugs, delivery techniques, or treatments.
   - Give a description of the experimental aspects of the study.
   - State the expected duration of participation in the study.
   - Describe briefly the procedures to be performed (e.g., lab evaluations, X-rays, office visits).
   - State the route of administration of the experimental agent.
2. Define RISKS attributable to the experimental agent and/or procedures.
3. Discuss any expected BENEFITS from participation in the trial.
4. Discuss ALTERNATIVE TREATMENTS.
5. State the policy for protection of CONFIDENTIALITY of records, noting that a qualified representative of the sponsor and the FDA may inspect subject study records.
6. Discuss whether COMPENSATION for study-related injuries is provided and if EMERGENCY TREATMENT will or will not be provided by the institution.
7. List the names and numbers of CONTACT PERSONS for research-related questions and for patient rights-related questions and questions regarding study-related injuries.
8. Clearly state that participation is VOLUNTARY and the decision to not participate or to withdraw from the study will not affect the patient's treatment plan.

Additionally, when appropriate the following items also must be included:

9. State that unexpected risks may be involved.
10. Discuss the circumstances under which the patient's participation may be terminated by the investigator or sponsor without the patient's consent.
11. Note that additional costs may be incurred by the subject due to study participation.
12. Inform the subject of the consequences of his/her decision to withdraw from the study.
13. Provide the subject with any significant new findings that relate to the subject's treatment and continued participation in the trial.
14. State the estimated number of subjects to be involved in the trial.

Other items to consider:

15. State that a copy of the Informed Consent Form shall be given to the subject.
16. The form should use terminology that the subject can understand.

In presenting the Informed Consent Form, the subject must understand what he/she is agreeing to. (See Chapter 6 for suggestions on presenting the informed consent process.)

Additional suggestions:

- Have the subject initial each page of the document.
- Keep the original in the study file or the subject's permanent record with a copy in the other file.
- Identify each version of the consent form by date or appropriate revision number.
- Note that if the informed consent is revised while the study is ongoing, subjects currently enrolled may need to sign the revised informed consent.

Special Groups

Specific considerations apply to certain groups and situations. Information can be found as indicated below:

Prisoners	21 CFR 50.40, 45 CFR 46 Subpart C.
Children	"General Considerations for the Clinical Evaluation of Drugs" and "General Considerations for the Clinical Evaluation of Drugs in Infants and Children"; 45 CFR 46 Subpart D; 21 CFR 50.25. FDA Information Sheet "Assent of Children Elements of Informed Consent."
Elderly	"Guidelines for the Evaluation of Drugs Likely to Be Used in the Elderly."
Women	"Evaluation of Gender Differences" (10/95); 45 CFR 46 Subpart B.
Veterans	41 CFR 16.

Also, be aware of special consideration involving the use of women of child-bearing potential in clinical trials. As the practice of in vitro fertilization and the use of fetuses for research increases, protection of rights of subjects should be addressed in these cases. The Belmont Report provides some background information to help understand the principles applied to the protection of human rights and how they may apply in these special circumstances.

Other Requirements

Note that certain state and/or local laws may also be in effect for the protection of subject's rights and safety. Investigate those requirements with the IRB.

Protection of Human Subjects

Everyone involved in research has a primary responsibility of protection of human subjects: their safety from harm due to study participation, their right to privacy, and their overall welfare. There are several federal offices that have oversight on the protection of humans in clinical research trials.

OHRP The Office for Human Research Protections was formerly called the Office for Protection from Research Risks. OHRP is located under the Office of Secretary of HHS. OHRP is charged with interpreting and overseeing implementation of the regulations regarding the protection of human subjects (45 CFR 46). OHRP also provides guidance on ethical issues in biomedical and behavioral research. OHRP has oversight and educational responsibilities wherever DHHS funds are used to conduct or support research involving human subjects.

OHRT The FDA has recently created a separate office to oversee subject protection, the Office for Human Research Trials. This office oversees and coordinates all human subject protection policy for industry-sponsored studies. OHRT participates in the FDA Bioresearch Monitoring Program (inspections), international GCP, and education activities.

OHSP The Office of Human Subject Protection is an NIH Intramural Research Program to provide oversight for the protection of subjects in clinical trials of the IRP.

REGULATORY REFERENCES

- 21 CFR 11, 50, 54, 56, 312; 45 CFR 46
- FDA Summary Sheets:
  - Informed Consent Regulations
  - Informed Consent and the Clinical Investigator (9/98) (see Table 2.1)
- The Belmont Report
- The Declaration of Helsinki (Helsinki Accord)
- ICH GCP Guideline

To obtain copies of the CFR, contact the local library or contact the FDA by calling 301-443-1382 for 21 CFR 50 and 56, and 45 CFR 46 Subparts A to D; 202-512-1800 for 21 CRF 312 and 314.50. All regulations, guidelines, and Information Sheets can be obtained through the Internet by contacting www.fda.gov. The ICH GCP Guidelines can be obtained directly from the FDA or from the FDA Web site.

CONTACTS

Office for Human Research Protections (OHRP)
[formerly Office for Protection from Research Risks (OPRR)]
6100 Executive Boulevard, Suite 3B 01 (MCS-7507)
Rockville, MD 20892-7507
301-496-7041

To obtain an IRB Guidebook, contact OHRP or ohrp.osophs.dhhs.gov/irb/

Federal Register: http://www.access.gpo.gov/su_docs/

IRBs can contact the following offices to determine whether an IND application or an Investigational Device Exemption (IDE) is required for the study of a drug or device:

Drugs

Document Management and Reporting Branch
Center for Drug Evaluation and Research (CDER)
301-443-4320
Fax on Demand: 800-342-2722 or 301-827-0577
www.fda.gov/cder

Biological Products

Division of Biological Investigational New Drugs
Office of Biologic Research and Review
www.fda.gov/cber
Center for Biologic Evaluation and Research (CBER)
301-443-4864
Fax on Demand: 800-835-4709 or 301-827-3844
www.fda.gov/cber

Medical Devices

Office of Device Evaluation
Center for Devices and Radiological Health (CDRH)
301-427-8162
Fax on Demand: 800-899-0381 or 301-827-0111
www.fda.gov/cdrh

To determine if a test article is a "drug" or "device"

Office of Health Affairs
301-443-1382

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Documentation Basics That Support Good Clinical Practices: The Master Plan. C. DeSain and C. Vercimak, *Applied Clinical Trials,* Vol. 2 (6), pp. 48–52, 1993.

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Women in Clinical Trials of New Drugs, A Change in FDA Policy. R. Merkatz, *New England Journal of Medicine,* Vol. 329 (4), pp. 292–296, 1993.

Women in Clinical Trials: Screening and Consent Issues Revisited. Terry Vanden Bosch, *Research Practitioner,* Vol. 1 (1), pp. 17–20, 2000.

Additional articles on subject informed consent are listed at the end of Chapter 6.

3

THE STUDY: PLANNING STAGES AND COMMENCEMENT

Preparing to do a clinical trial takes a lot of work before the first subject is enrolled. The key to a successful study is careful planning. The protocol and study design need to be concise, clear, and feasible as well as provide the data to prove (or disprove) the objectives of the study. All of the details of conducting the study must be worked out ahead of time, not in the midst of subject visits. The more that can be anticipated prior to initiation of a trial, the more likely the trial will proceed (relatively) smoothly. Once the trial has started, it is necessary to keep organized and to continue problem solving of those situations that inevitably "pop up." Termination of the trial is a time to put all things in order to store away for future reference.

PROTOCOL DEVELOPMENT

Before you can conduct a study, you must have a protocol—a written, detailed PLAN for how the study will be conducted and analyzed. Protocols are developed and written in a variety of ways; it is rarely an individual effort. First, the authors must determine what information is known and what has been discovered by previous trials. In the development of a new drug by a sponsor, there is usually an overall drug development plan for the drug, and the content of the protocol is largely determined by that plan. Other things to consider are as follows:

- What phase is the trial?
- What is the disease, and what aspect of the disease is being examined?
- Will there be a control group (active, placebo, observation only, standard treatment)?
- What study design(s) should be used (parallel, crossover, "washout," "lead in," single blind, double blind, open label)?

A variety of resources may be used when preparing the protocol: research articles on similar trials, the Investigator's Brochure, similar protocols, the drug development plan. Other physicians, project leaders, Clinical Research Associates (CRAs), Clinical Research Coordinators (CRCs), statisticians, and pharmacists all make contributions to the production of a protocol, which is the study plan.

Chapter 1 provides details on the specific sections of a protocol.

THE PLANNING STAGES OF A STUDY

Before an institution agrees to conduct a clinical trial, it is crucial that the study be evaluated and initial planning be in progress. In collaboration with the investigator, the CRC should evaluate the following aspects of the study.

Protocol

Review the protocol with the investigator and sponsor:

- Is it a good protocol? Is it logistically feasible to conduct at the study site?
- Determine whether the study can be done at your institution per protocol and discuss the potential trouble spots. It is important to solve potential problems before the study commences.
- Use the protocol to begin making contacts and planning with the pharmacy, inpatient/outpatient units, clinical laboratory, electrocardiogram (ECG), X-ray, and so on.
- Evaluate the available patient population. (See the section "Study Subject Recruiting" in Chapter 6.)

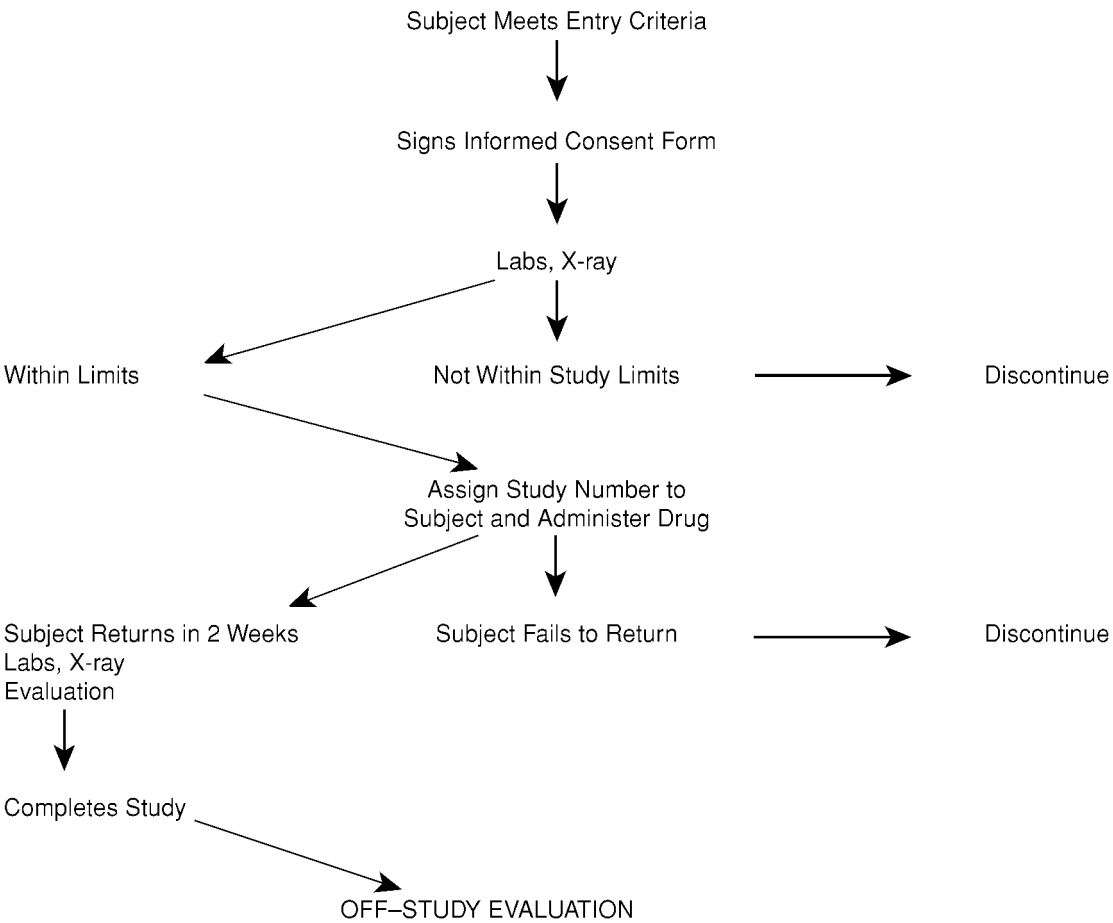
An especially useful part of the protocol is a graphic schedule of visits and evaluations (Appendix D) and a study schema (Figure 3.1). If they are not included in the protocol, create these two tables.

Budget

Can the study be done at your institution with the money allocated?

- Make a list of all costs after each group (pharmacy, lab, etc.) has read the protocol and submitted its budget to you.

FIGURE 3.1 SCHEMATIC DIAGRAM OF STUDY ENTRY AND GUIDELINES



- Can you get discounts for a certain volume of tests done?
- Are outside agencies cheaper or more reliable for certain study services (labs, X-ray, etc.)?
- Be sure you understand where all costs come from—do you or the company sponsor pay for photocopying, mailing, duplication of X-rays, and so on? Be sure to include these figures in your budget proposal.
- What is your institution's fee for administrative overhead?
- Prepare a sample budget based on a per-patient cost (Table 3.1) and compare to the money allocated by the sponsor. You should at least break even.
- Reevaluate the study budget after the study begins in order to identify any extra costs incurred.

- Usually, patients who participate in studies pay only for the care they would normally receive if they were not on a study. Any study-related tests or procedures are covered by the study budget. Be sure you understand what is "customary care" for these patients so that the budget will be reasonable.
- Assure that billing is handled in such a way that patients are not billed for study procedures.
- Clarify the basis of reimbursement with the sponsor.
- Are screening costs covered for subjects not enrolled?
- Are only evaluable subjects reimbursed? Precisely how is an evaluable subject defined?
- Who pays for miscellaneous costs such as photocopying, mailings, etc.?
- Determine the payment schedule with the sponsor. Usually, payments are made in increments depending on subject enrollment and completion. The following is an example:
  - 25 percent total amount as an initial payment
  - 25 percent when half of the subjects are enrolled
  - 25 percent when all subjects are enrolled and at least half have completed
  - 25 percent at the conclusion of the trial after the final study report is submitted

In determining a payment schedule, make sure you can cover your costs—especially if it involves subject reimbursement.

Work closely with the grants administrator at your institution. This is the person who actually handles the money.

Pharmacy

Often a pharmacy will be used to store the investigational agent, and arrangements need to be made. Table 3.2 provides a worksheet to assist in planning with the pharmacy. Items to consider include the following:

- Will the institution pharmacy be used?
- Who will be the pharmacist in charge of the study? Establish good communications early in study planning.
- The pharmacy may submit its budget (usually standardized by the institution).

TABLE 3.1 BUDGET PLANNING WORKSHEET

PROTOCOL _____

ANTICIPATED NUMBER OF SUBJECTS _____

		Cost per Subj (# subjs)	Total
Screening			
Clinical Laboratory:	CBC		
	Blood Chemistries		
	Urinalysis		
OTHER, specify:			
ECG			
X-rays			
OTHER evaluation:			
Professional time (exams, interviews)			
Consultation, specify:			
Screening Total			

Interim Visits (begin with enrollment visit)		Required # Visits	Cost per Subj (# subjs)	Total
Clinical Laboratory:	CBC			
	Blood Chemistries			
	Urinalysis			
OTHER, specify:				
ECG				
X-rays				
OTHER evaluation:				
Professional time (exams, interviews)				
Consultation, specify				
Hospitalization (# days)				
Total				

Table 3.1 continued on next page

Table 3.1 continued from previous page

	Required # Visits	Cost per Subj (# subjs)	Total
Other Costs			
Special Equipment, specify:			
_____			_____
_____			_____
_____			_____
_____			_____
_____			_____
Supplies, specify:			
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	
_____	_____	_____	_____
Pharmacy	_____	_____	_____
Subject Compensation	_____	_____	_____
Secretarial/Clerical Support			_____
Advertising			_____
Clinical Research Coordinator (estimated # hours times base salary)			_____
Copying, Mailing, etc.			_____
Institutional Overhead (_____% of total)			_____
Other Costs Total			_____

Totals

Screening Total	_____
Interim Visit Total	_____
Other Costs	_____
Total Cost of Study	

- Check for drug storage capabilities—per the protocol. Will drug volume be large? Will the drug need to be mixed, requiring additional supplies and cost? What are the storage requirements (out of light, refrigerated)?
- Are the pharmacy services available on weekends, holidays, or during non-business hours?
- What is its drug destruction policy?
- Do they have their own forms that they prefer to use for drug accountability? How does this compare with the sponsor's form?
- Consider the study drug's shelf life, shipping and receiving requirements, and satellite pharmacy interactions.
- Is the study drug dispensed as unit dose, infusion, by bottle, carton, card, or other?
- Are there study-specific pharmacy procedures? Who will be responsible for these?
- Is there a randomization code? Will the pharmacist be responsible for randomizing patients? In blinded studies, will the pharmacist need to unblind the code for preparation of the study material?
- Will there be a code breaker? If so, who will have it, and under what conditions should the code be broken? Is there someone available 24 hours a day to break the code in an emergency?
- If the pharmacy is not being used for the study drug, evaluate the alternative storage area:
  - Is it locked and secured?
  - Does it meet the storage requirements of the drug?
  - Is the temperature monitored?
  - Is it accessible by study personnel?
  - Who will have access?
  - Who will have responsibility for dispensing and maintaining the study drug?

TABLE 3.2 CLINICAL INVESTIGATION INFORMATION FORM FOR THE PHARMACY

Title of Study _____

Principal Investigator _____ Telephone _____ Pager _____

Department _____

Subinvestigators _____

Clinical Research Coordinator _____ Telephone _____ Pager _____

Sponsor _____ Contact _____ Telephone _____

Name of Investigational Agent

		Dose	Frequency	Route
#1	_____	_____	_____	_____
#2	_____	_____	_____	_____
#3	_____	_____	_____	_____
#4	_____	_____	_____	_____

How supplied: _____

_____

Storage requirements: _____

_____

Study design (check all that apply):

- ☐ Randomized
- ☐ Single blinded
- ☐ Double blinded
- ☐ Open label
- ☐ Crossover

Randomization Code: _____

Code Breaker ☐ Yes ☐ No

Subjects: ☐ Inpatient ☐ Outpatient ☐ Day Hospital

Number anticipated: _____

Sites receiving investigational drug other than hospital/clinic: _____
(supply mailing addresses and contact persons on separate page) _____

To Be Completed by Pharmacy:

Responsible pharmacist _____ Telephone _____ Pager _____

Who will be responsible for the following:

	Pharmacy	Investigator	Other	N/A
Drug storage	☐	☐	☐	☐
Randomization	☐	☐	☐	☐
Drug preparation	☐	☐	☐	☐
Drug dispensing	☐	☐	☐	☐
Accountability records	☐	☐	☐	☐
Inventory control	☐	☐	☐	☐
Shipping drug to other sites	☐	☐	☐	☐

Clinical Laboratory, ECG, X-ray, and Other Clinical Departments

- Establish one individual as your contact person for each department.
- Determine the cost of studies performed and try to find the most economical way of ordering tests (for example, it is often less expensive for a lab to run an automated blood panel than it is for them to test for only certain parameters, e.g., a chemistry panel vs. just sodium and potassium).
- Will there be a code or special requisition forms to assure the test is billed to the study account and not the patient? You may need to establish an account for the study.
- What are the weekend/holiday/daily hours for availability and/or sample pickup? You may need to arrange a different lab setup when patients are seen on days when the regular lab is closed (i.e., using the ER lab on weekends).
- Obtain laboratory licenses and/or certifications, normal value ranges, and the CV of the lab director. Collect this documentation on EACH lab you will be using. Periodically assess the lab for license renewals and changes in normal value ranges.

Medical Records

Find out the policy for obtaining, reviewing, and duplicating patient records (hospital medical records as well as clinic charts). These may require a signed permission form from the patient ahead of time. Additionally, determine the policy for retention of patient records. These are considered source documents for the study and must be maintained as long as study files.

Administrative

- Arrange for a backup person to be available if you are the only CRC on the study. Instruct this person on the basics of the trial and orient him/her to all of the study information materials (protocol, procedure manual, special forms, etc.).
- Meet with all subinvestigators and additional CRCs to organize your efforts and to have everyone working from the same plan.
- Arrange an "in-service" meeting with hospital staff.

Regulatory

- Write the Informed Consent Form and obtain sponsor approval.
- Submit protocol, informed consent, and any proposed advertising plan to the IRB.
- Complete, sign (by Principal Investigator), and submit to the sponsor the Statement of Investigator form (Form FDA 1572) and appropriate curriculum vitae.

The Paper Trail

The CRC will often be in the middle of the crossfire of documents for study start-up. The CRC *may* be involved in the paper shuffle of the following:

- Contracts and/or Indemnification Agreements.
- Budgets.
- Regulatory documents (1572, CVs).
- IRB documents (approvals, Informed Consent Forms).
- Laboratory documents.
- Many others!

STUDY COMMENCEMENT

After what may seem like endless preparation, the time has come for entering the first patient. Is everything ready? You say, enthusiastically, "YES!" but think, "well, I *hope* so . . . ." A general checklist of completed preparations may look something like this:

- Protocol is finalized (at least for now).
- Regulatory paperwork is completed.
- Ancillary services are ready (lab, X-ray, pharmacy, etc.).
- The investigational agent is in-house and ready to be dispensed.
- Nursing or other personnel on whose ward or clinic you may be conducting the study have been in-serviced or trained in study procedures.
- You have a payment "advance" or initial grant payment or at least have adequate funding to get started.
- Case Report Forms (CRFs) or flow sheets are ready.
- Your study work areas have been reserved for your use and are equipped as necessary.

A study start-up checklist is provided in Table 3.3.

TABLE 3.3 STUDY START-UP CHECKLIST

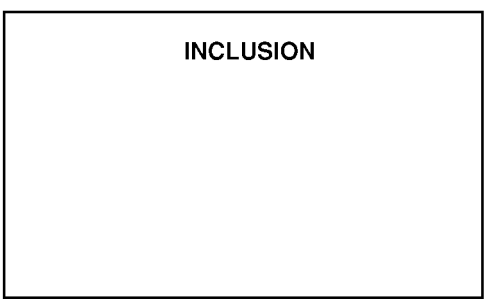
Completed		Sent to Sponsor
☐	Signed confidentiality agreement	☐
☐	Contract agreement with sponsor	☐
☐	Indemnification agreement	☐
☐	Statement of Investigator completed	☐
☐	Curriculum Vitae prepared	☐
☐	Protocol reviewed and signed	☐
☐	Informed Consent Form prepared	☐
☐	Protocol and Informed Consent Form to IRB	
☐	List of IRB Membership	☐
☐	IRB meeting date _____	
☐	IRB approvals received	☐
☐	IRB renewal date _____	
☐	Clinical Laboratory certification on file	☐
☐	Clinical Laboratory normal values on file	☐
☐	List of key site personnel with signatures	☐
☐	Receive and review study procedure manual	
	Arrangements made with:	
☐	Pharmacy	
☐	Clinical laboratory	
☐	In-house ward	
☐	Clinic scheduling	
☐	Other departments _____	
☐	_____	
☐	_____	
	Evaluate subject population:	
☐	Develop a recruitment strategy	
☐	Prepare advertising	
☐	Submit advertising to IRB	☐
☐	Notify subjects	
☐	Prescreening clinic	
	Budget:	
☐	Prepare	
☐	Internal approval	
☐	Submitted to sponsor	☐
☐	Sponsor approval	
☐	Initial payment received	
	Supplies received:	
☐	Case Report Forms	
☐	Investigational Agent	☐
☐	Clinical Lab Supplies	
☐	Special Equipment	
☐	Shipping materials	
☐	_____	
☐	_____	

Some helpful hints to keep in mind:

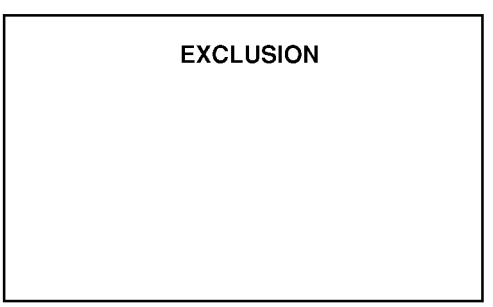
- *Stay organized.* You may wish to keep a copy of the protocol with you at all times until you feel that you have all aspects memorized.
- *Highlight areas of importance* on your copy of the protocol for quick reference.
- A set of handy *cue cards* for your pocket are a tremendous help. Write out *3 × 5 cards* to help get started and to keep vital information and phone numbers at your fingertips (see Figure 3.2).
- A *schematic* of the study (Figure 3.1 on page 59) or schedule of events calendar (Appendix D) are useful aids.
- Keep telephone numbers of everyone you may need on a card in your pocket. You will use it often.
- Color code your cards, group them—whatever makes your efforts more organized for you. Be creative!

FIGURE 3.2 3 × 5 CARD EXAMPLES

Inclusion/Exclusion Criteria (list)



front



back

The Protocol Violation

Don't be afraid to ask questions as you are entering the first patients. Despite all of your careful planning, things may still go wrong when it comes to actual implementation. You may make a mistake in protocol requirements (referred to as a "protocol violation") or miss a data point on your first subject or two. This is a new experience for all involved, and some bumps along the path to the protocol's success are expected. But, CORRECT your problems as soon as possible and PREVENT the same mistakes for the next study subject. If the protocol is very complicated, it may be constructive to pause after entering one or two subjects to meet and discuss the progress and problems with the study team. If problems are still not getting resolved, enlist the assistance of the company sponsor representative.

How to Get Along with Everyone

As the CRC, you will be interacting directly with the subjects, their families, and medical personnel.

Medical Personnel

Some staff will enjoy participating in clinical research and will gladly cooperate to help get the study going. Others will see it as unnecessary work and effort on their part and will do everything possible (it may seem) to make your job difficult. Try to be fair, keep a sense of humor, and remain focused on the task at hand. *Wear your diplomacy hat at all times*. Try to make a compromise when possible to keep the peace, and *listen* to the criticism—some may be quite valid and could require procedural modifications on your part. Keep the investigator aware of any problems you are having and ask him/her to intervene if you reach an impasse. Don't get into arguments with people whose cooperation you need to get the study done.

Subjects and Families

Be sure to obtain a truly *informed* consent. Does the subject really understand what he/she is signing? Is he/she aware of all the tests/procedures involved? A subject who feels misled may not comply with the study or may drop out.

Be sure subjects have a way of contacting you during the study if they have questions. Give clear directions, written and illustrated, if appropriate, and guide them step-by-step through the study. Point out to subjects not only the risks of participating in the

study but also the potential and real benefits. Telephone calls as reminders before study appointments can be helpful. It's that little extra attention that can keep a subject interested and cooperative. Refer to Chapter 6, "The Role of the Study Subject," for more information.

KEEPING UP WITH THE STUDY

Now that you've got the study going, how do you keep things running smoothly? There is so much to keep organized; all of that paperwork to attend to; and, of course, the subjects. First, get your priorities straight: The subject should always come first, as long as you stay within the guidelines of the protocol. Subject scheduling and appointments should be the first consideration on your things-to-do list.

Next, **designate a backup person** to assist you or to handle the study in your absence. Keep him/her informed on all developments in the study.

Also, you need to tackle all of that paperwork on a regular basis or it gets out of control. Here are some suggestions:

- SCHEDULE time for paperwork and don't let anything interfere.
- Keep CRFs and data flow sheets current, both for data accuracy and data management.
- Don't let the "to be filed" pile get out of control. Try to file things as you go along.
- Set up a filing system that is easily accessible (desktop) to automatically deposit things where they need to be (e.g., lab results, X-rays, IRB, sponsor) instead of one big "to be filed" pile where it becomes impossible to locate anything.

Other suggestions for staying organized:

- Keep a calendar just for the study; write in dates for scheduled and projected subject visits, monitoring site visits, due dates (IRB progress reports, annual renewal), investigational drug reorder dates, study staff meetings, and so on.
- Make and use checklists, charts, note cards, or whatever system works for you to stay ahead.
- Keep current versions of the Study Procedures Manual, Protocol, and other study aids close by for easy reference.

- Keep patient materials (lab requisitions, appointment cards, etc.) nearby for easy access.
- Keep each individual subject's paperwork in a separate file.

Starting the study is only the beginning. There are a number of things that need to be done on a regular basis:

Study Files

The study files must be set up and kept current. The sponsor monitor should review the study files periodically during monitoring visits. A study documentation checklist is included in Table 3.4. Section 8 of the ICH GCP Guideline provides a concise outline of essential documents for the conduct of clinical trials.

IRB Correspondence

In addition to the initial contact with the IRB, the investigator must communicate with the IRB during the study in specific cases:

- Annual renewals.
- Progress Reports (frequency determined by the IRB).
- Submission of Protocol Amendments.
- Revised Informed Consent Forms resulting from amendments or safety reports.
- Reports of serious adverse events at the site.
- Reports of serious adverse events (IND safety reports) at other sites.
- Final Study Report.

Investigational Agent

Documentation for the investigational agent must be kept current (refer to Chapter 9, "Investigational Agent Management"). The supply of investigational agent must be monitored to assure that an adequate stock is available for subjects enrolled in the trial as well as new subjects. DON'T RUN OUT! In some studies, it may be necessary to collect and store the tear-off labels from the containers. You may also have to receive, organize, and store investigational agent returned by subjects in the trial. It will help if you create a study-specific tracking chart of investigational drug for each subject and attach it to the subject's record.

TABLE 3.4 STUDY DOCUMENTATION CHECKLIST

- ☐ Form FDA 1572
- ☐ Curriculum Vitae
- ☐ IRB Approvals and Correspondence
  - Submittal package
  - Initial approval letter
  - Progress Reports
  - Annual renewals
  - Protocol Amendments
  - IND Safety Reports
  - Final Report
- ☐ Correspondence between Investigator and Sponsor and other study-related correspondence
- ☐ Informed Consent Forms
  - Blank copy of all IRB–approved versions
  - Original signed copies of study participants' Informed Consent Forms
- ☐ Protocol
  - Original signed version
  - All amended versions
- ☐ Investigator's Brochure
  - All versions applicable to the study
- ☐ Investigational Agent Shipping Records
- ☐ Investigational Agent Dispensing/Accountability Records
- ☐ Investigational Agent Final Disposition Records (documenting return of drug to sponsor, destroyed, or all used in study)
- ☐ Case Report Forms
  - Blank copy of all versions
  - Completed and signed copies for each study participant
- ☐ Serious Adverse Event Reporting Forms (blank)
- ☐ Reports of Serious Adverse Events (IND Safety Reports)
- ☐ Study Progress Reports and Final Report
- ☐ Clinical Laboratory Certification
- ☐ Clinical Laboratory Normal Value Ranges
- ☐ Study Procedures Manual
- ☐ Telephone Monitoring Records
- ☐ Monitoring Log

Maintain separately:

- ☐ Budget
- ☐ Indemnification and Study Contracts

Case Report Forms

CRFs should be completed immediately after a subject's visit. Some pages may be completed during the study assessment visit; in this case, make sure there is adequate documentation in the subject's medical record/clinic chart to use as source documentation. Don't let completion of the CRFs become backlogged . . . it's a tough hole to dig out of! Also, the CRFs must be current for the site monitoring visit so that the monitor can review all of the CURRENT data. You also may have to make copies of the CRFs or separate NCR papers to submit the data to the sponsor. The sponsor may also require that data on CRFs be faxed directly to the sponsor to speed up data entry and analysis. If you are using remote data entry, the same concept applies . . . keep up with data entry. Also, be sure to generate hard copies of the data and file them immediately.

Budget

Follow the budget closely. Make sure the sponsor is initiating payments as agreed (note there will probably be some lag time for administrative preparation and mailing of payments—allow four weeks). Work with the grants administrator. Ensure that the bills are getting paid. You may find that your original arrangement is not working. You may have to be creative and borrow from other resources or renegotiate your arrangement with the sponsor.

STUDY TERMINATION

Have heart; most studies do end (although they never go away). At that time, there's much cleanup work to do.

Subjects

It's time to say good-bye to your subjects, at least in terms of the trial. The subjects may be part of your patient population, and you may see them again for regular clinic visits. If they have been recruited solely for participation in this study, arrange for record transfer to referring physician. Make sure all final assessments are done. Resolve all compensation issues with the subject. Instruct them to return all study-specific materials, such as investigational agent, monitoring apparatus, and so on. Make sure you have a way to contact the subject (maintain a confidential patient log of subject names, addresses, and phone numbers) should anything about the study arise that requires notification. If the subject was compliant, consider using him/her or recommending him/her for other trials.

Investigational Agent

All study drug must be returned to the sponsor or properly disposed of as indicated by the sponsor (see Chapter 9, "Investigational Agent Management"). This includes all unused drug, all returned drug and containers, and tear-off labels, if applicable. Additionally, ensure that the paperwork is intact. Place the original shipping records, invoices, subject drug accountability (dispensing) logs, and disposition forms in the permanent study file. If the pharmacy requests to keep the originals, a copy should be placed in the study files with a memo explaining the location of the original records. Code breakers should also be filed in the study files.

Informed Consent Forms

The original signed informed consent for each subject should be stored in the study files. If it is not possible to keep the original in the file (e.g., it is required to be in the patient's Medical Record), then a copy can be placed in the file with a memo describing the

reason and where the original may be located. A blank copy of each version of the Informed Consent Form used in the study should be kept in the study files.

Data

All data must be completed and submitted for data analysis. This should occur as quickly as possible. Copies of subject CRFs or data flow sheets should be maintained and stored with the study files. Data queries may continue long after the study has ended.

Study Files

Now is the time to go through the study files AGAIN and assure that everything is there and all unnecessary articles are removed. A study documentation checklist is included in Table 3.4. The files should be boxed for storage (unless there is adequate storage space in the filing cabinet). Locate the final resting place for these files and show the location to the monitor during the termination visit. Also, record the location somewhere so that, years later, anyone with the need (such as during an FDA inspection) will be able to locate the files. CLEARLY mark the box with the study number, title, investigator, and who to contact.

Final Report to the Sponsor and IRB

A final report must be written and submitted to the IRB and the sponsor (generally, the sponsor will hold the final payment until the final report is filed). Different IRBs require different elements to include in the report. Some general items are as follows:

- Number of subjects enrolled.
- Number of subjects completing.
- Number of subjects dropping out and reasons.
- Frequently noted adverse events.
- Serious adverse events.
- Subject deaths, if any.
- Investigator's opinion of the results.

IRB In addition to the final report, the IRB should also receive formal notification of completion of the study. This might be incorporated into the submission of the Final Report.

Study Supplies All study supplies (CRFs, study specific lab requisitions, sample collection materials) must be returned to the sponsor (or destroyed if so designated by the sponsor). Equipment purchased or supplied by the sponsor may be returned or may be made available for general use at the sponsor's discretion.

Budget Prepare information for the final payment. Ensure that all bills are paid.

Table 3.5 is a checklist for study termination activities. Table 4.4, "The Termination (Study Close-Out) Site Visit" (in Chapter 4), also will help in preparing to close the study.

TABLE 3.5 STUDY TERMINATION CHECKLIST

Subjects:
- ☐ Complete final assessments
- ☐ Return and inventory investigational agent
- ☐ Return study materials
- ☐ Obtain address
- ☐ Resolve compensation

Investigational Agent:
- ☐ Inventory all drug, used and unused
- ☐ Resolve all accountability issues
- ☐ Assemble files, "paper trail"
- ☐ Prepare investigational agent for inventory by sponsor
- ☐ Prepare tear-off labels, randomization cards, code-breakers for inventory
- ☐ Complete accountability logs to indicate return/destruction of drug
- ☐ Package and return investigational agent
- ☐ File paperwork relating to final disposition (returned to sponsor, destroyed, used in trial)

Data:
- ☐ Record all data on CRFs or data flow sheets
- ☐ Submit to investigator for review and *signature*
- ☐ Assure subject's medical record/clinic charts are available and accurate for source document verification
- ☐ Maintain copies of all CRFs or data flow sheets in study files
- ☐ Generate and file hard copies of final data reports if remote data entry is used
- ☐ Return or destroy all unused CRFs
- ☐ Resolve queries related to data entry

Regulatory:
- ☐ Inventory and file all signed Informed Consent Forms in the master study file
- ☐ Prepare and submit Final Study Report to IRB and sponsor
- ☐ Notify IRB of study termination

Study Files:
- ☐ Organize study files (see study file checklist)
- ☐ Consolidate all files into a master study file to be stored
- ☐ Box master study file
- ☐ CLEARLY label the storage box
- ☐ Make a notation of the storage location of the master study files/notify sponsor

Study Supplies:
- ☐ Return or destroy unused CRFs
- ☐ Destroy study-specific lab requisitions and labels
- ☐ Return or release study-specific supplies (e.g., collection tubes, packaging materials)
- ☐ Return special equipment, if required
- ☐ Return remote data entry equipment

Biological Samples:
- ☐ Inventory all samples
- ☐ Ship for analysis as indicated by the sponsor

Budget:
- ☐ Assure final payment is received from sponsor
- ☐ Assure all bills are paid

Sponsor:
- ☐ Schedule and prepare for termination site visit (see Table 4.4)
- ☐ Resolve all outstanding issues

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4

INTERACTIONS WITH THE SPONSOR

Many clinical trials are conducted by "sponsors." The sponsor is typically a pharmaceutical company but may also be a Contract Research Organization (CRO) working for the sponsor or a government agency (e.g., NCI) or a cooperative research group (e.g., NSABP, SWOG). The pharmaceutical industry sponsor's objective generally is to get a new drug to market or to establish new applications for an existing drug. These pharmaceutical research activities are closely observed by the U.S. Food and Drug Administration (FDA), and approvals are contingent on studies that are appropriately designed and completed. Additionally, FDA regulation states that the sponsor will monitor the clinical trial [21 CFR 312.56(a)]. The sponsor, therefore, will closely monitor the progress of a clinical trial.

The frequency of monitoring will vary depending on the phase of the study, type of study, study progress, amount of data, deadlines, and so on. Communication between the Clinical Research Coordinator (CRC) and the sponsor is critical to the success of the trial. Typically, the contact person for the sponsor is the Clinical Research Associate (CRA). The most effective means of assuring that a clinical trial is conducted properly is to conduct site visits. Telephone communication, investigator meetings, and written correspondence are other methods of communication between the sponsor and the clinical site.

Studies are also funded by grants from specific research organizations. The funding organization may be considered the sponsor in these situations. Their requirements for Good Clinical Practice (GCP) and adherence to FDA regulations is similar to that of the pharmaceutical industry. However, the monitoring process may not be as intense.

This chapter focuses on the pharmaceutical sponsor, but the general concepts apply to all types of studies.

SITE MONITORING VISITS

The most significant interactions between the CRC and the sponsor occur during site monitoring visits. There are four basic types of site visits:

1. **Prestudy:** The sponsor and investigator are evaluating the possibility of doing the clinical trial together. This stage may also involve protocol development.
2. **Initiation:** The study is ready to begin, and both parties are ascertaining the readiness of the clinic to start enrolling patients. The visit is instructional in the procedures of the study. Sometimes, it may be planned to enroll the first subject in conjunction with the initiation visit.
3. **Periodic:** The study has started, and the sponsor visits the site regularly to ensure that the study is being conducted according to protocol and FDA regulations, there are no problems with the study site, Case Report Forms (CRFs) are being completed appropriately, and there are no unreported serious adverse events.
4. **Termination or study close-out:** The study is over—all documentation is in place, all data have been submitted, all investigational supplies returned to the sponsor, and all outstanding questions are addressed.

Another type of site visit is a *preinspection* visit. Often, when an investigator is notified of an inspection by the FDA, the sponsor will return to the site to review the study materials with the investigator and help prepare for the inspection.

Quality assurance audits may be conducted by the sponsor to assess not only the site's performance but also that of the monitoring staff. See Chapter 10 for a discussion of quality assurance audits conducted by the sponsor.

Careful preparation is required by both parties to assure that site visits are effective for both the site and the sponsor. Tables 4.1–4.4 summarize preparation steps for a site visit.

RESOLUTION OF PROBLEMS IDENTIFIED AT SITE VISITS

At the end of each site visit, the CRC should meet with the monitor to discuss the findings. Remember that the study is a team effort, and everyone is working toward the same goal. The monitor has the experience of working with other sites, often on the same studies, and may have valuable suggestions as to how to improve the way the study is conducted. Additionally, it is the responsibility of the monitor to assure that

- the study is being conducted according to protocol,
- FDA regulations are adhered to, and
- subject safety is monitored.

The monitor and the CRC should try to resolve problems or identify solutions to problems prior to the monitor's leaving the site. Outstanding problems are likely to be documented in a follow-up letter to the investigator. DOCUMENT RESOLUTIONS TO ANY OF THESE SITUATIONS IN WRITING.

It is desirable to resolve all data queries on the CRFs at the time of the site visit. However, because of time constraints, the monitor may leave questions noted in the CRFs requiring resolution or clarification. These may be indicated on a data audit checklist or with yellow Post-it® notes. Reconcile these questions as soon as possible and forward the corrected CRFs to the sponsor.

The ICH GCP Guideline discusses specific responsibilities of monitoring the clinical trial in Section 5.18.

GRANT–SPONSORED VISITS (AUDITS AND INSPECTIONS)

Cooperative Research Bases, as well as other sponsors, must monitor their clinical trials for quality assurance based on appropriate execution of the trial and quality of the data. Ancillary areas important in the conduct of the trial, such as pathology or radiotherapy, may also be monitored. Often grant approval, or reapproval, is contingent on a site inspection. Monitoring practices may differ from one group to another. It is best to prepare for these visits by following the guidelines set forth by the grant-issuing body, as well as those given in Tables 4.1–4.4.

TABLE 4.1 THE PRESTUDY SITE VISIT

OBJECTIVE

Sponsor To assess the study site and the investigator's ability to perform the clinical trial. In this evaluation, the sponsor will be reviewing the investigator's previous research experience, the availability of patients/volunteers, the ability to do the study at the facility, and personnel support.

Investigator To learn about the study, investigational drug, and sponsor; assess the logistics of conducting the trial at the facility; and propose possible changes to the protocol. (Note: The CRC may or may not be involved in the prestudy visit.)

PREPARATION

The investigator and his/her staff prepare for the prestudy site visit by the following steps:

- REVIEW the protocol, Investigator's Brochure (IB), and CRFs by all pertinent staff with comments returned to the Principal Investigator (PI) prior to the visit.
- Present the PI's CREDENTIALS (and those of key staff) to the sponsor—generally through a *current* curriculum vitae (CV).
- Evaluate training and experience of other participants (CRC, pharmacy, laboratory technician, etc.).
- Present the ORGANIZATIONAL STRUCTURE of the personnel at the facility.
- Assess the SUBJECT POPULATION and provide information on where and how subjects will be recruited as well as an estimate of the number of study participants available.
- Arrange for a tour of the FACILITY. Included should be areas key to the conduct of the trial, especially:
    - exam rooms/areas where subjects will be treated/evaluated;
    - laboratory facilities;
    - special testing facilities;
    - pharmacy (main pharmacy and applicable satellite pharmacies);
    - in-hospital areas, if hospitalization required;
    - work areas for staff;
    - administrative areas; and
    - storage areas for study supplies.
- Prepare an AGENDA for the meeting with the sponsor. (Often, the sponsor will suggest an agenda.)
- Reserve a MEETING ROOM and assure that *all* relevant staff can attend.
- Prepare a BUDGET for conducting the clinical trial.

Table 4.1 continued on next page

Table 4.1 continued from previous page

DOCUMENTATION

The following documents may be presented or collected prior to or during the prestudy site visit:

- CONFIDENTIALITY AGREEMENT: A statement signed by the investigator on behalf of his/her staff to keep all study information confidential. This form is customarily executed prior to receipt of the protocol, IB, and other documents.
- CLINIC VISIT RECORDS: The PI may substantiate that he/she has access to the needed patient population by producing clinic records, hospital census, or other appropriate information.
- PREVIOUS STUDIES: The PI may discuss previous trials done by him/her at the facility to establish expertise.
- CURRICULUM VITAE: The CV may be presented to establish the PI as an expert in the field.
- BUDGET PROPOSAL: A budget proposal may be requested by the sponsor either for the site visit or as a follow-up to the site visit.
- STATEMENT OF INVESTIGATOR (Form FDA 1572): This form should be reviewed prior to or during a prestudy visit and information completed so that the investigator understands the obligations set forth by the FDA regulations and GCP guidelines.

FOLLOW–UP

If both the sponsor and the investigator agree to proceed with the clinical trial, the following items need to be done:

- Read and sign the Statement of Investigator form (Form FDA 1572) and send to sponsor with CV of each person named therein.
- Draft Informed Consent Form. Submit to sponsor for review.
- Submit final protocol and Informed Consent Form to the Institutional Review Board (IRB) for approval. Send IRB approval and copy of informed consent to sponsor.
- Make arrangements within institution to begin seeing study patients (study logistics).
- Sign Indemnification and Study Contract Agreements, if needed.
- Obtain clinical laboratory certifications and normal ranges and send to the sponsor.
- Prepare for arrival of study supplies.
- Finalize budget.
- Set up initiation meeting. Plan to attend any Investigator's Meeting/Workshops.

TABLE 4.2 THE SITE INITIATION VISIT

OBJECTIVE

Sponsor To prepare the site personnel to perform the clinical trial. May include specific training, review of materials, attendance at an Investigator's Meeting. Assure all regulatory documentation is completed, study logistics worked out, drug at site, and subjects identified.

Investigator To review all aspects of the study to assure proper implementation. All required regulatory documentation completed, study logistics worked out, drug at site, and subjects screened and identified.

NOTE: At times, the first subject may be enrolled in conjunction with the initiation visit (or another site visit) while the sponsor is on-site.

PREPARATION

The investigator and his/her staff prepare for the initiation visit by the following steps:

- The FINAL PROTOCOL should have been reviewed and study logistics determined. Any outstanding questions should be addressed during the initiation visit for clarification. Note that any major changes to the protocol at this point are likely to delay the start of the trial.
- All STUDY DOCUMENTS should have been completed/obtained and filed in the study files. Additional items that may be required prior to study initiation are the Clinical Study Agreement (the contract between the sponsor and investigator/institution) and the Indemnification Agreement. Generally, it is up to the investigator to request these agreements from the sponsor, and they often are handled through the corresponding legal departments. Note that even minor disagreements in these legal contracts can greatly delay the beginning of the clinical trial.
- The INVESTIGATIONAL AGENT should have arrived at the site and be ready for inspection by the monitor.
- Review STUDY PROCEDURES MANUAL, if one is being used.
- Review CASE REPORT FORMS so that you can ask questions regarding the completion of the CRFs.
- Screening of subjects may have already occurred. If so, present a list of POTENTIAL SUBJECTS (identified by initials) to the monitor.
- Be prepared to show the FACILITIES to the monitor, including work area, patient visit areas, blood drawing areas. Make appointments with appropriate ancillary personnel, e.g., the pharmacist, to meet with the monitor.
- If the first subject is to be treated during this visit, be sure to schedule this as part of the visit.

Table 3.3 in Chapter 3, "Study Start-Up Checklist," will assist in preparing for the initiation site visit.

DOCUMENTATION

The following documents should be submitted to the sponsor PRIOR TO the initiation site visit:

- Signed 1572 and CVs for investigator and subinvestigators.
- IRB approval letter.

Table 4.2 continued on next page

Table 4.2 continued from previous page

- IRB approved Informed Consent Form.
- Signed copy of the final protocol.
- Clinical Laboratory Certification/Laboratory normal ranges.
- Indemnification Agreement/Study Contract Agreement.
- Final Budget.
- List of key site personnel with signatures.

FOLLOW–UP

If there are no outstanding issues between the sponsor and the site, subject enrollment may begin.

- Notify sponsor of first subject enrolled.
- Inform the sponsor of any problems that occur AS THEY OCCUR.
- Establish the date for the first periodic site visit.

If there are outstanding issues between the sponsor and the site, these need to be resolved (and the resolution documented, generally by a letter) prior to subject enrollment.

TABLE 4.3 THE PERIODIC SITE VISIT

OBJECTIVE

Sponsor To assure that the study is being conducted according to protocol and FDA regulations and that the clinical trial is progressing smoothly. Specifically, this includes the following:

- FDA regulations and GCP guidelines are being followed.
- Subject safety is being assessed.
- The protocol is being followed.
- Drug dispensed appropriately/blind maintained/accountability records completed and current/drug inventory agrees with log.
- CRFs completed/verify data per original source documents (medical record, charts, lab reports)/CRFs signed by investigator after thorough scrutiny.
- Entry criteria are met.
- Informed Consent Form signed for each subject prior to screening.
- Protocol violations identified and discussed.
- Subject accrual rate adequate.
- Subjects compliant.
- Facilities remain adequate.
- Assess for changes in personnel.

Investigator To cooperate with the sponsor to meet the above objectives. To discuss or resolve any study-related problems.

PREPARATION

The investigator and the CRC prepare for the periodic site visit by the following steps:

- Keep CASE REPORT FORMS current. Have the investigator review and sign all completed CRFs prior to the site visit.
- Have all CRFs, MEDICAL RECORDS, and CLINIC CHARTS available in a designated work area for the monitor to review.
- Have all INFORMED CONSENT FORMS available for review and verification.
- If a SERIOUS ADVERSE EVENT was reported, have all information available for review and verification.
- Keep DRUG ACCOUNTABILITY RECORDS current.
- Make an appointment with the PHARMACIST to review drug accountability records and shipping records and to inventory the investigational agent(s). If required, have all tear-off labels, randomization envelopes, and/or code breakers available for the monitor to check to assure that study blinding is maintained.
- Have STUDY FILE DOCUMENTS available and filed appropriately.

Table 4.3 continued on next page

Table 4.3 continued from previous page

- Set up an appointment, generally toward the end of the visit, for the monitor to meet with the INVESTIGATOR to discuss findings of the site visit.
- Adjust your CALENDAR so that you have time to meet with and work with the monitor to resolve discrepancies.

DOCUMENTATION

- Any NEW documentation—such as IRB reapprovals, lab recertifications, updates to CVs, or changes to the Statement of Investigator—will be collected by the monitor.
- Signed INFORMED CONSENT FORMS will be reviewed.
- Information pertaining to an IND SAFETY REPORT may be collected.
- Completed and signed CRFs will be taken to the sponsor offices by the monitor.

NOTE: In many cases it will be necessary to photocopy the CRFs or separate NCR forms; allot time accordingly. Some sponsors will take all CRFs back to the company offices and have copies made and returned to the site. The site *must* retain a copy of every CRF submitted.

FOLLOW–UP

All discrepancies identified during the periodic site visit must be resolved and the resolution documented (usually by a letter to the sponsor or in the monitor's site visit report).

Often the monitor will leave comments for clarification on the CRFs. These issues need to be resolved as soon as possible.

TABLE 4.4 THE TERMINATION (STUDY CLOSE–OUT) SITE VISIT

OBJECTIVE

Sponsor To assure that the study is completed, all study supplies and investigational agents returned to the sponsor, all documentation in place, all data (CRFs) accurate and returned to the sponsor; to discuss the requirements for retention of study materials.

Investigator In addition to the above objectives of the sponsor, the investigator may want to know the results of the study, what the plans for publication may be, what future trials he/she may be involved in, and compensation issues.

PREPARATION

The investigator and his/her staff prepare for the termination site visit by the following steps:

- Review the STUDY FILES for completeness and accurate filing.
- Consolidate all RECORDS into one set of study files. (Refer to Table 3.4 in Chapter 3, "Study Documentation Checklist.") Prepare to box the files for storage.
- Complete and have the investigator review and sign all CRFs. There should be no outstanding data queries at the end of the termination site visit, although queries may continue when the data are processed by the sponsor. Copies of the CRFs must be maintained with the study documents.
- Assure that the subjects' MEDICAL RECORDS and clinic charts are available for the monitor to verify data and address queries.
- Have all subjects' signed INFORMED CONSENT FORMS available for review and storage with the study records.
- Resolve any outstanding DISCREPANCIES identified on previous periodic site visits.
- Complete the FINAL STUDY REPORT for submission to the IRB and sponsor.
- Notify the IRB of study completion or termination.
- Establish an AGENDA for the monitor's site visit. Make appropriate appointments.
- Review BUDGET agreement to determine outstanding compensation.
- Review INVESTIGATIONAL AGENT accountability records. Have all shipping forms available for review. Have access to all study drug, randomization cards, and tear-off labels, if used for the study. Organize study drug according to
    - unassigned drug,
    - assigned but undispensed study drug, and
    - study drug returned by subjects.
- Organize the study drug and tear-off labels by subject number to facilitate inventory of the investigational agent. Have material available to pack the investigational agent for return to the sponsor. Alternatively, if the sponsor permits, arrange to have the investigational agent destroyed on site by an acceptable means. The monitor may be required to witness the destruction of the investigational agent.
- Arrange for the return of STUDY SUPPLIES (unused CRFs, clinical laboratory supplies, etc.). Remove any preprinted clinical laboratory requisition forms that are specific for this trial.

Table 4.4 continued on next page

Table 4.4 continued from previous page

- Inventory any BIOLOGICAL SAMPLES collected for the study and determine their disposition.
- Arrange for the monitor to meet with the INVESTIGATOR at length to discuss study termination activities, the final study report, outstanding discrepancies or problems, arrangements for compensation, requirements for retention of study records, publication policies, instructions for responding to a request for an audit by the FDA.
- Clear your CALENDAR to be available to meet with the monitor.
- Arrange for a CONTACT PERSON for the monitor to resolve any additional discrepancies and data clarifications of CRFs that occur at a later date.

Table 3.5 in Chapter 3, "Study Termination Checklist," will assist in preparing for the study termination site visit.

DOCUMENTATION

The following items may be collected during the termination site visit:

- Updates to regulatory documents.
- IND Safety Reports (adverse drug experience reports), if any.
- Final Study Report.
- New or missing correspondence.
- Drug accountability records (one copy for the sponsor, originals to the study files unless the pharmacy requests to keep the originals, in which case a copy should be placed in the study files with a memo explaining the location of the original records).
- CRFs.

Other items collected:

- Biological samples.
- Unused and returned investigational agent.
- Unused study supplies and CRFs.

FOLLOW–UP

- Resolve any outstanding discrepancies identified during the termination site visit and document the resolution.
- Assure that all clinical trial supplies and investigational agent are returned to the sponsor or appropriately disposed of.
- Store study documents in an acceptable area as discussed with the monitor.

TELEPHONE MONITORING

The CRC and the sponsor also communicate by telephone. It is important that the CRC feel comfortable in contacting the sponsor of the trial to resolve questions or report new findings. Telephone discussions, particularly when they involve decisions regarding the conduct of the trial or the handling of subjects, should be documented. This can be accomplished in one of many ways:

Telephone Monitoring Reports — A detailed report is written and filed in the study files. It may be initiated by the monitor, the CRC, or both. If each party writes a report, the content should be consistent. The other party to the discussion may request a copy of the report. An example of a report form is in Figure 4.1.

Telephone Logs — A log is maintained with entries of each telephone contact. Key information may be noted in the log. An example is in Figure 4.2.

Follow-Up Letters — A letter is written to confirm decisions made during the telephone conversation. They may be initiated by either the monitor or the CRC.

WRITTEN CORRESPONDENCE

Many items are documented through written correspondence between the investigator (or CRC) and the sponsor. All of this correspondence must be retained as part of the study file records. Additionally, any other correspondence regarding the clinical trial such as internal memos, E-mail, correspondence to other sites, and labs also must be retained in the study files.

FIGURE 4.1 TELEPHONE MONITORING REPORT

NAME OF SITE REPRESENTATIVE _____

NAME OF SPONSOR REPRESENTATIVE _____

CALL INITIATED BY ☐ SITE ☐ SPONSOR

DATE _____ TIME _____

PROTOCOL TITLE _____

PROTOCOL NO. _____

INVESTIGATOR _____

REASON FOR CALL (check all that apply):

☐ subject accrual	☐ protocol	☐ order supplies
☐ subject dropout	☐ administrative	☐ shipment of samples
☐ adverse event	☐ investigational agent	☐ data clarification
☐ IND safety report	☐ blind broken	☐ other _____
☐ subject death	☐ personnel/facility change	☐ _____
☐ protocol violation	☐ problem with lab	☐ _____

DISCUSSION:

SIGNATURE _____ DATE _____

cc: Principal Investigator
Sponsor representative
original to study files

FIGURE 4.2 TELEPHONE MONITORING LOG

PROTOCOL TITLE _____

PROTOCOL NUMBER _____

INVESTIGATOR _____

Date	Site Representative	Sponsor Representative	Discussion

Store with study files.

What Should Be Documented by Written Correspondence or Telephone Contact?

The discussion of specific issues relating to the administration and conduct of the clinical trial should be documented for the study records. These items may include, but are not limited to, the following:

Study Administration	IRB approval status. Informed consent process. Budget. Study files and documentation.
Protocol	Entry criteria. Drug dosages/modifications. Randomization and blinding procedures. Protocol violations (notify sponsor immediately). Protocol amendments.
Accrual	Randomization to study groups. Accrual rates/goals. Withdrawals/dropouts. Subject registration.
Case Report Forms	Status of completion. Clarifications/answers to queries. Shipment to sponsor. Requests for copies. Storage of CRFs.
Adverse Events	Clinical management. Reporting abnormal lab values. Reporting trends. Reporting Serious Adverse Events to the FDA. Subject deaths.

Data	Reporting of efficacy data. Interim reports of subject data. Data clarification forms.
Investigational Agent	Ordering/shipping/disposition. Storage. Coding/randomization. Recall or retesting for potency. Breaking the study blind (revealing the code).
Clinical Supplies	Ordering/storage/shipping.
Biological Samples	Collection. Storage/shipping. Labeling. Analysis/results.
Facility Changes	Clinic. Hospital. Pharmacy. Clinical or analytical laboratories. Pharmacy/study supply/study files storage areas. New satellite sites.
Personnel Changes	New investigator/subinvestigators (especially around June/July in major medical centers). Change in Clinical Research Coordinator. Change in pharmacists. Change in Clinical Research Associate.

INVESTIGATOR'S MEETINGS

An Investigator's Meeting may be held at the beginning of a clinical trial to allow group discussion of the study and drug development plan or review of current data. CRCs often participate in these meetings. When the meeting is study specific, the format is

similar to a prestudy site visit where the protocol and study design are discussed; study logistics also may be addressed, and CRFs may be reviewed.

Additionally, an Investigator's Meeting may be scheduled during the middle of a large trial for many reasons: to discuss findings and work through logistics, to assure consistency across sites, and to increase enthusiasm about the study.

STUDY PROCEDURES MANUALS

Many sponsors or coordinating CRCs will prepare a Study Procedures Manual delineating all of the specific procedures for a clinical trial. Generally, the procedures manual will include additional, more detailed information on conducting particular aspects of a study. If the sponsor does not provide a manual and you are coordinating a large trial with many interacting people, it may be a good idea to prepare a brief manual for all involved. Some topics to include:

Regulatory Requirements	A summary of regulations and/or a current copy of 21 CFR 312, 50, 56.
Entry Criteria	Inclusion/exclusion criteria (as a checklist or directly from the protocol or CRF).
Schedule of Visits	A graphic representation of scheduled study visits and evaluations (see Appendix D).
Study Schema	A schematic presentation of the study process.
Protocol	A current copy of the protocol. (Be sure to update this copy as amendments are received.)
Special Tests	Instructions for conducting special tests or assessments. For example, Central Radiology Review: directions on how to obtain radiological studies and transmit the studies on film, optical disk, or by electronic data transfer.

Rating Scales	Any special rating scales, performance status scales, lesion scoring guidelines, and so on should be included.
Toxicity Grading Scale	The toxicity grading scale from the protocol should be used.
Completion of CRFs	Guidelines for completing CRFs or flow sheets (see Chapter 7) with samples.
Investigational Agent	Guidelines on handling the investigational agent, completing accountability records, instructions to subjects.
Collection of Biological Samples	Special instructions for the collection, storage, and shipping of biological samples.
Serious Adverse Events	Information and instructions for reporting a serious adverse event (see Chapter 8).
Subject Death	Measures to take in case of a subject death (see Chapter 8).

An article in the ACRP newsletter, *The Monitor*, written by Deborah Thompson, a CRA for many years, succinctly summarizes the interaction between the CRC and CRA:

> A key ingredient of any successful study is a good working relationship between the Clinical Research Coordinator (CRC) at a site and the Clinical Research Associate (CRA) assigned to that site. In fact, the successful outcome of a study—meeting timelines and obtaining valid data—may well depend on it.
>
> I recently conducted an informal survey of CRAs and CRCs, and both identified three very fundamental principles for establishing a good working relationship:
>
> 1. Mutual respect for each other's role in the study, recognizing that we are all part of the same team, working toward the same goal. Although our roles are very different—performing the study vs. monitoring the study performance—each complements the other.

Given the very nature of monitoring, which involves pointing out inadequacies and errors and clarifying discrepancies, it is easy to forget the purpose of monitoring:

to ensure that FDA requirements for conducting clinical research are met;

to ensure that the study is conducted according to protocol; and, above all,

to ensure that patient safety and rights are maintained.

2. Trust in each other's knowledge and capabilities.

Both CRAs and CRCs go through intensive training programs in order to perform their job at the highest level of skill possible. Without knowing what the other's job fully entails, it is not always possible to see why certain actions were taken or requested in all situations. We both need to remember that asking for an explanation doesn't suggest doubt in the other's judgement or knowledge but merely serves to clarify what may not be immediately understood.

3. Positive communication.

Many CRCs indicated that what they most appreciate from a CRA is clear and consistent instruction. Although the protocol stands as the reference when in doubt, the CRC relies most on the CRA for guidance and clarification. Some helpful suggestions given by CRCs include the following:

Providing instructions with the rationale behind them, instead of merely stating "Here's what you do," makes them easier to remember.

Following up on any complicated situation in writing helps to further eliminate any ambiguity.

Knowing the CRAs expectations from the very beginning saves both the CRA and CRC a great deal of time and frustration later on, as does remaining consistent with those expectations.

As in any working relationship, both sides must listen to what the other is experiencing so that when problems do arise, realistic solutions can be implemented.

As CRAs, we need to remind ourselves that a CRC may initially view us as strangers invading their territory. Encouragement and assistance rather than criticism and demands will help to build rapport with the site and make the clinical trial a positive, successful experience for everyone.

from CRA-CRC Relationship. Deborah Thompson, "CRA Monitor's Notes," *The Monitor*, September, pp. 11–17, 1993. Reprinted by permission.

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5

INTERACTIONS WITHIN THE INSTITUTION

The Clinical Research Coordinator (CRC) is often responsible for coordinating activities within the institution when implementing study logistics. These include interactions with the Principal Investigator (PI) and subinvestigators, clinic and in-house scheduling offices, clinical and special laboratories, and other departments (e.g., ER [emergency room], ICU [intensive care unit], and Radiology Department), as well as the grants administration office and the Institutional Review Board (IRB).

THE PRINCIPAL INVESTIGATOR AND SUBINVESTIGATORS

The PI is ultimately responsible for communications regarding the clinical trial. However, it is often the CRC who is more intimately involved with the details of the study. It is imperative that there be open communication and clear delineation of responsibilities between the PI and CRC. Also, essential study information must be disseminated to all subinvestigators to assure that the study proceeds as smoothly as possible and according to protocol. Table 5.1 provides suggestions to facilitate communication about the study to all research staff involved.

THE INSTITUTIONAL REVIEW BOARD

The policies of IRBs at each institution may differ. The CRC will need to become familiar with the policy of the institution. However, all IRBs are required to adhere to FDA regulations (see Chapter 2 and Appendix A, 21 CFR 56).

At some institutions, the investigator and/or CRC are requested to attend the meeting of the IRB when their project is being discussed. At others, the investigator/CRC may

TABLE 5.1 FACILITATING STUDY COMMUNICATION

Schedule regular, periodic meetings with the PI and subinvestigators to discuss the trial.

- Circulate a draft agenda prior to the meeting and request that participants submit items for the agenda.
- Stick to the agenda at the meeting but also allow time for unanticipated items.
- Some suggested areas to discuss: Patient accrual, adverse events, responses, amendments or changes to the study, information from the sponsor, specific problem areas.

Submit regular periodic reports to the PI.

Particularly, you may want to keep the PI updated on such things as accrual rates, adverse events, specific problem areas.

Develop a centralized computer database that study personnel can access.

Have multiple copies of the protocol, study procedures manual, study schema, and relevant study aids available for all study personnel.

Keep additional copies in areas where they may be easily obtained, e.g., central office area, clinic exam rooms, etc., but remember to maintain confidentiality by limiting access.

Develop study aids.

Develop charts, flow sheets, study schemas, schedules of evaluations and visits, study pocket cards (see Figure 3.1, Table 7.1, and Appendix D), forms, graphs, and lists that easily communicate aspects of the study.

be asked to not attend if their research is being discussed unless he/she is needed to clarify questions. In any case, an investigator/subinvestigator who sits on an IRB may not vote on any research in which he/she is involved.

The IRB needs to be updated periodically on the progress of the study. The IRB must be notified of Serious Adverse Events and patient deaths (see Chapter 8). Also, IRBs require at least an annual progress report (sometimes more frequently, depending on the risk involved and IRB policy) and renewal of approval at the anniversary of the initial approval date. The investigator is required to submit all amendments to the protocol (modifications to the research study) to the IRB and obtain approval of the amendment prior to implementation. Amendments affecting subject safety, i.e., removing a hazard, may be implemented prior to IRB notification but must be submitted in a timely matter.

Maintain all documentation of communication with the IRB in the study file. Chapter 2 discusses the regulations as they pertain to interactions with the IRB.

STUDY LOGISTICS

One of the major responsibilities of the CRC is working through the logistics of study implementation, i.e., the day-to-day activities of performing a clinical trial. Working through the study logistics is probably the most critical task in a clinical trial. It is possible that the protocol may require changes because it would not be feasible to do something as written. This usually requires a great deal of organization, cooperation, ingenuity, and, sometimes, a little coercion!

- **When:** Study logistics should be evaluated at some point between the prestudy visit and prior to the initiation visit. The CRC should be prepared to walk-through the procedures at the initiation visit with the monitor.
- **What:** Table 5.2 contains some of the areas that the CRC will need to coordinate within the institution.

Most of these items are discussed in greater detail in other areas of the handbook. Refer to Chapters 3 and 4 for additional information on study procedures involving other areas of the institution.

PREPARING HOSPITAL STAFF

Often, it will be necessary to conduct the clinical trial in a hospital setting where hospital staff will be involved. The nursing staff involved must be informed of the study procedures. Some ways to accomplish this are as follows:

- Have an in-service meeting to discuss the study. Be specific about what responsibilities the nursing staff will have—administering the test agent, observing for adverse events, collecting vital sign data and test samples.
- Provide standard Physician's Orders for study subjects.
- Provide a protocol-specific checklist to attach to the subject's chart/daysheet. It is helpful to use a distinctive color of paper to set the list apart from all other chart papers.
- Let the subject know what the study-specific procedures are—the subject may be able to remind the staff of sampling time when necessary.
- Discreetly label the subject's chart, daysheet, bed, wristband (anything and everything that makes sense!) to alert staff that this is a study subject.

TABLE 5.2 AREAS OF INSTITUTION COORDINATION

TASK	DESCRIPTION
Administrative Functions	Includes IRB approvals, advertising, study file maintenance.
Subject Screening	How will study subjects be identified and screened? Will special screening clinics be arranged?
Subject Referrals	Notify appropriate specialty areas within the institution for subject referrals. Are subjects to be identified or enrolled through such areas (e.g., ER, CCU)?
Subject Visits	How are visits to be scheduled? Is there adequate space? Plan the subject's day . . . how will the visit flow from assessment to labs to special tests, etc.?
In-House Subjects	If subjects are to be admitted to the hospital, what will the procedure be? Notify all staff on the floor of specific study procedures. Place brightly colored instruction sheets in the subject's chart.
Subject Billing	What arrangements are made to assure the subject is not billed for procedures that are study related?
Obtaining Lab Tests	Will the lab be available for tests during subject visits? Is it close by? Will it create a bottleneck in the flow of the subject's visit? Can priority be given to study subjects?
Medical Records	Are medical records readily obtainable? How much lead time is needed? How long are medical records maintained by the institution? Does this meet regulatory requirements for record retention? Per FDA regulations, source documents must be kept for the same time period as study files. What happens to a subject's file after a death?
Completing Medical Records	Determine what is necessary to include in the subject's medical record or clinic chart. Is an *original* signed Informed Consent Form required (the subject may need to sign many copies)?
Dispensing Investigational Agent	Will the investigational agent be dispensed through the pharmacy? If so, is it open at the time of subject visits? Will the pharmacy be responsible for randomizing subjects? Does the pharmacy keep the code-breaker? Is a pharmacist available 24 hours in case of an emergency? Is the pharmacist qualified to dispense drug; does he/she know the study? Where and how will the drug be stored? Will the pharmacist maintain records as required?
Other Sites	Sometimes your institution will be the coordinating site for a large multicenter trial or a cooperative group effort. In this case, who will be responsible for shipping study drug, screening and enrolling subjects, coordinating data?
Tests Done by Other Departments	How will subjects be scheduled? How will the department be compensated? Will someone consistently be reading the test? What is the report turnaround time and mechanism?
Subject Compensation	Will subjects be compensated? How? Is compensation contingent on study adherence and completion?
Grants Management	Is there a specific department in the institution that handles all grants? What is its role? Does it make payments as well?
Legal Issues	The legal department may be involved with negotiating contracts and indemnification agreements.

- Provide prelabeled sample collection vials and other study-specific materials.
- Develop a team approach with the staff and be sure to follow up periodically so that any errors or omissions can be caught early and corrected.

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6

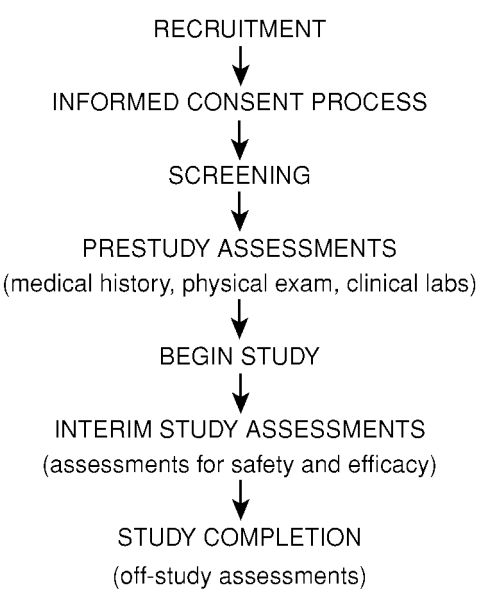
THE ROLE OF THE STUDY SUBJECT

The most essential element of a clinical trial is the study subject. The type of subject required for the trial is defined very specifically in the protocol by the inclusion/exclusion criteria. Subjects must be recruited for enrollment into the study and, once enrolled, must remain motivated to participate throughout the entire study. Interactions with study subjects is another key responsibility of the Clinical Research Coordinator (CRC).

THE SUBJECT

The role of the study subject in a clinical trial can be expressed schematically, as in Figure 6.1, which presents a very simplified version of a study subject's participation; many things can, and will, happen along the way.

FIGURE 6.1 ROLE OF THE STUDY SUBJECT



What motivates people to participate in clinical trials? In a survey done at Virginia Commonwealth University, the main reason cited why healthy adults volunteer to participate in Phase I clinical trials was money. The reason individuals did not agree to be in subsequent studies was schedule conflicts (1).

There are other reasons why people enroll in a clinical trial:

- Recommended by physician as a treatment option.
- Free medical care.
- Free medicine.
- No other treatment options.
- Provide therapy that may improve health or prolong life.
- Altruism.
- Education.

Whatever the motivating factor, it is important to keep the subject motivated for participation, from the recruiting phase through study completion.

STUDY SUBJECT RECRUITING

Recruiting and enrolling study subjects is critical to the success of the clinical trial. Enrollment into the clinical trial needs to occur in a timely fashion for a variety of reasons:

- The research needs to be completed while the scientific question is relevant to make the most of the window of opportunity.
- The sponsor is often in a race to get to market with the new treatment.
- In multicenter trials, recruitment and subject entry should be equitable across sites to retain scientific validity of different geographical areas.
- Recruitment delays result in increased costs for recruitment, increased study costs, and an increase in time to complete the study.
- Compensation is often based on the number of subjects. In a multicenter trial, you may be in a situation of competing for study dollars, and you may be shut out if your accrual rate lags behind other sites.
- The longer it takes to accrue into a study, the more likely it is that the baseline characteristics of the subjects will differ.
- Personnel and administrative changes may occur over a longer accrual time.

- Completion of the study cannot be in sight until all subjects are recruited and enrolled.

Since the preplanning stage of the study is such a critical time, the following items should be taken into consideration during the accrual period:

- Establish an accrual period and *stick to it*. Set short-term and interim accrual goals so that progress can be monitored and problems can be detected and corrected early.
- Be realistic (even conservative) about the number of patients you can enter. In an early paper (1975), Ederer suggested that any estimate of potential subjects should be divided by ten (2). In another retrospective survey, it was estimated that it is necessary to screen twice as many subjects as are needed to complete the study (3).
- Take into account the amount of time required for screening subjects. How many subjects can you reasonably process?
- Start prescreening as soon as possible to assess what percentage of your anticipated subject population can actually qualify for the intense screening phase and ultimately participate.
- When reviewing potential subjects from medical record and clinic chart reviews, be sure that the information is current, complete, and accurate.
- Have a contingency plan in case you are unable to fulfill your accrual requirement with your initial population.
- Clinical Research Units and private Phase I units should have a person who specializes in recruiting subjects.
- Check with other sites that are recruiting successfully. What are their secrets?

Finding Study Subjects

The first step in locating subjects is to compile a list of potential candidates. Although it will vary by study, there is a variety of resources to examine when compiling a study subject contact list:

- Review hospital medical records/database.
- Review hospital daily census.
- Review clinic records/database.

- Review subjects enrolled in previous similar clinical trials ("pool" of subjects).
- Advertise (see section on advertising).
- Check support group rosters.
- Seek referrals from local physicians.
- Seek participation by university students.
- Recruit coworkers (institution personnel).
- Hold screening clinics.
- Check subjects not considered for similar studies who may fit the criteria for this trial.
- Remember to respect subject privacy and access only information for which you are authorized.

When subjects are identified, aggressively contact them by telephone or letter to discuss the study.

Advertising

Advertising for study subjects is often successful. Advertisements can take many forms: posters, leaflets or pamphlets, newspaper ads, study aids (e.g., a laminated study pocket card with information about the study eligibility criteria), educational material, and others. REMEMBER, all advertising must be submitted to the IRB for review and approval. Care must be taken not to be coercive. Here are some suggestions for advertising a clinical trial:

- Place newspaper ads (select the section of the paper carefully to best target your subject group).
- Publish a newspaper article concerning the research project with a "who to contact" line at the end. If you cannot entice the press to come to you, issue a press release through the institution.
- Advertise on local free or cable TV or radio.
- Place posters and/or leaflets in the clinic waiting area.
- Place posters and/or leaflets throughout the institution.
- Design a study pocket card with study information and eligibility criteria (see Figure 6.2) and distribute to medical professionals (in your institution and others) who regularly come in contact with your patient population.
- Solicit referrals from local physicians: Send a letter explaining the study or, better yet, make personal visits to their offices. Provide posters/leaflets for the

waiting area. Leave study pocket cards (see Figure 6.2). Enlist their support and assure them subjects will return to them for routine care. Compensation for referrals must be considered carefully and may be considered unethical in certain instances.

- Attend a meeting of disease-specific support groups at which you give a presentation, provide a poster, or hand out leaflets.
- Advertise in special interest publications/newsletters.
- Advertise in specialty stores, pharmacies, and hospital supply stores.
- Advertise at local colleges and universities, especially for young, healthy, normal volunteers.
- Advertise at senior citizen gatherings for older, healthy volunteers.
- Gain community support and enthusiasm.
- Set up a booth at health fairs.
- Recruit industry support: Advertise at selected companies and enlist their support through incentives such as time off for study visits, recognition for participation (however, be careful not to be coercive).
- Spread the word! Have study participants and colleagues tell their friends; they may even be able to carpool for visits!
- Plan a direct mail campaign or telephone campaign, contacting potential subjects directly. Be careful to consider patient confidentiality.
- Arrange for the clinical lab to send a follow-up mailing to subjects or their physicians whose lab results fit your criteria (or to supply you with a mailing list—but be careful of confidentiality requirements).

Be Aggressive

FOLLOW UP ON ALL LEADS BY TELEPHONE CONTACT OR LETTER.

For example, periodically call local physicians to remind them about the study; send reminder postcards; follow up referrals with thank-you letters and progress reports. Examples of study pocket cards, letters, and ads can be found in Figures 6.2–6.4.

FIGURE 6.2 SAMPLE STUDY "POCKET CARD"

DIABETES STUDY

ELIGIBILITY:	newly diagnosed diabetic patients between 35 and 55 years old
INCLUSION CRITERIA:	AODM, may not be insulin dependent
EXCLUSION CRITERIA:	chronic illnesses requiring medication

CALL 555-5555, C. Menow, CCRC, for details or to refer patients.

These cards can be made small enough to fit in a lab coat pocket and can be laminated for durability.

FIGURE 6.3 SAMPLE LETTER TO PHYSICIANS REQUESTING REFERRALS

Dear Dr. _____:

Dr. Knowall at Major Medical Center is conducting a clinical trial to assess the effect of an experimental treatment on newly diagnosed diabetics (AODM). We are looking for newly diagnosed diabetics who fit the following criteria:

Age: 35–55 years old
Insulin dependent less than 6 months or noninsulin dependent
Have no other chronic illnesses requiring medication
Available to participate in study for 2 years
Three separate overnight stays required

Patients will continue to see their primary physician for all care; specific protocol guidelines will be provided to you. Additionally, all clinical laboratory results obtained from the study will be provided to the subject's primary physician. Subjects will receive compensation for expenses, blood glucose monitoring supplies, and $100 for each overnight stay.

Please contact C. Menow, CCRC, at 555-5555 for details or to enroll patients.

Thank you,

FIGURE 6.4 SAMPLE AD FOR NEWSPAPER

ATTENTION: NEWLY DIAGNOSED DIABETICS

YOU MAY QUALIFY FOR A RESEARCH TRIAL FOR THE TREATMENT AND MANAGEMENT OF DIABETES!

- Learn about your disease
- Free medication
- Free medical monitoring
- Participants receive a free glucometer to monitor blood glucose
- Reimbursement for expenses (parking, time from work)

Requirements: 35–55 years old, healthy, noninsulin dependent
Call Dr. Knowall at 555-5555, Major Medical Center

Making Participation Attractive

Many factors can affect recruitment and ultimate enrollment into the trial. Take the following into consideration when planning your study:

Study Design

- How long a period is participation in the study?
- How frequent are the visits?
- How intense are the visits?
- How uncomfortable are the study measurements?
- How stringent are the inclusion/exclusion criteria? Can they or should they be relaxed now rather than later if you cannot meet accrual goals?
- Is a placebo being used? Will subjects be motivated to participate if they receive a placebo?

Incentives

- Free medical care.
- Free health-risk screening and monitoring.
- Compensation (payment) for participation.
- Reimbursement for expenses.
- Free drug (e.g., Retrovir® in HIV trials, antibiotic in strep throat study).

Patient and Family Attitudes

- Is the patient optimistic and enthusiastic about study participation?
- Enlist support of family and friends of subject to assist in compliance.

Informed Consent

- The subject should be educated about his/her disease and study participation.
- How the study is presented to the subject may greatly influence the decision to enroll. Always be honest and open; answer all questions. (See the following section on obtaining informed consent.)

Investigator

- An experienced investigator will know the ins and outs of recruiting subjects.
- The investigative staff needs to be familiar with the subjects and supportive throughout the trial, and sometimes afterward.

Competing Studies

- Know your competition—are there any other studies currently enrolling your subject population?
- Avoid doing multiple trials yourself that require the same subject population.

Timing

- What time of day are your screening efforts? Consider that the majority of people work during the day. Plan screening (and follow-up) according to the potential subject's schedule. You may be doing some evening and weekend work. Or recruit through companies; screen on-site.
- Consider the disease—is it seasonal, as in many allergy studies? Maximize your recruiting efforts during the peak of the season.
- Vacation, summer, and holidays are slow recruiting times.
- "Take the show on the road," such as to the job site or local support group meeting, if this will facilitate recruitment and follow-up.

Response to Ads

- When advertising, be sure that the potential subject is able to get through when calling (e.g., use an answering machine on a line *dedicated* to call-ins).
- Be enthusiastic on your answering machine message ("Thanks for showing interest in our study").
- Return calls quickly.
- Be knowledgeable about the study; be prepared to give the potential subject the information most important to them—how much time, compensation, number of visits, and so on.
- These calls will set the mood for future interactions with the subject. Choose your words carefully.

Treat the Subject Well at the Screening Visit

- Avoid long waiting times for tests.
- Walk the subject to different parts of the institution for testing procedures.
- Serve coffee and donuts—as long as they don't interfere with the study parameters!

In summary, plan well ahead and develop a recruiting strategy for the clinical trial. Expect recruitment delays. Consider your study design at the outset—if the criteria are too strict, you, in discussion with the sponsor, may have to loosen the criteria, which results in lost time and potential subjects. Keep in mind that recruiting of subjects may continue while other subjects are returning for follow-up visits. Consider the logistics and plan accordingly so that the clinic schedule is not overloaded. Set accrual goals, especially for long-term studies, and attempt to keep an even accrual pace.

OBTAINING INFORMED CONSENT

Generally, the development of the Informed Consent Form is the responsibility of the investigator. Often the CRC is instrumental in the process. Often, in pharmaceutical-sponsored studies, the sponsor will provide a template. In many cases, the IRB reviewing the study will have a template or specific instructions for the contents of the Informed Consent Form. The NCI has a template that is used for NCI–sponsored studies (and other cooperative groups?).

The process of presenting the provisions of informed consent can affect a subject's decision to enroll in the study. When all of the elements are included, the Informed

Consent Form can sound very scary. Be honest with the subject at all times, but be careful not to frighten the subject away. For example, to a subject who raises a concern over the adverse events listed on the Informed Consent Form, the CRC may respond, "Yes, you may be concerned about the adverse events, but we will be monitoring you very closely to avoid or treat any serious event. You would also expect those same symptoms if you were taking Brand X, the approved treatment for this disease." The CRC must be knowledgeable about the study, the investigational agent and similar treatments for the disease, and the disease itself.

When: The subject should be presented with the Informed Consent Form at the beginning of any assessment or screening for study participation. While it is imperative that the Informed Consent Form be signed prior to any study-specific procedures or prior to receiving a test agent, it is preferable to present the informed consent to the subject at the outset of consideration so that the subject is aware that the process involves research and is informed of options. Note that this may occur after a lab panel or a medical history has been taken for clinical purposes. It is acceptable to use such data as long as it is not testing that is required for the study that is outside normal clinical practice; such procedures are study related and require informed consent prior to implementation. Elements required for Informed Consent Forms are discussed in Chapter 2.

Why: It is a regulatory and ethical requirement to inform subjects about participation in clinical trials.

Who: Generally, the PI or the CRC presents the Informed Consent Form to the subject. Minimally, that person should be knowledgeable about the study so that he/she is able to answer any questions the subject may have. Additionally, he/she should be able to assess the subject to ascertain that the subject fully understands what is being agreed to.

How: The way in which the informed consent process is conducted is critical to subject participation and may affect study recruitment. Some steps to follow are as follows:

1. Discuss the study with the subject in general terms. Outline the purpose, procedures, and time commitment.
2. Give the subject a copy of the Informed Consent Form to read. Also, with the subject's approval, give a copy to any family member accompanying the subject. Allow the subject ample time to read through the document.
3. *Read through* the Informed Consent Form with the subject. Stop at each section to ask if the subject understands and if he/she has any questions.

4. At the end, again allow the subject to ask questions or raise concerns.
5. If the investigator is not the person presenting the informed consent process, then he/she should ideally make time available to talk to the subject to see if there are any concerns or, at the very least, be available to discuss the study with the subject if the subject so requests.
6. When the subject indicates that he/she fully understands the Informed Consent Form, ask him/her to sign the document. Note that it may be necessary for the subject to sign multiple copies of the Informed Consent Form. Other signatures, such as the PI, person presenting the informed consent process, or a witness may be required. These signatures should be obtained at this time on all copies.
7. Give the subject a copy of the Informed Consent Form to keep for his/her own information.

It is important to keep the following factors in mind when presenting the informed consent process to the subject:

- The Informed Consent Form must be APPROVED by the IRB. Only the most CURRENT approved form may be used.
- The Informed Consent Form should be CLEAR, DIRECT, AND SIMPLE to understand. Avoid research or technical terms.
- The Informed Consent Form should be given to the subject to read, and then it must be EXPLAINED AND DISCUSSED THOROUGHLY with the subject. All questions must be answered to the satisfaction of the subject.
- Make sure the Informed Consent Form is in a LANGUAGE that the subject understands.
- In some instances, e.g., with illiterate subjects, it may be necessary to READ the Informed Consent Form to the subject and then obtain his/her signature on the form. These types of informed consents *must* be witnessed.
- "SHORT FORM" Informed Consent Forms generally indicate only that the trial was discussed with the subject and the subject agrees to participate. A written summary of what is said to the subject must be provided. A witness must be present and sign *both* the summary and the Informed Consent Form. The subject must receive a copy of the summary and the Informed Consent Form.
- A VIDEOTAPE showing the procedures and other study-related items may facilitate the process.

- Explain the RISKS AND BENEFITS completely. You may need to respond to questions regarding the probability of any specific risk to the subject. KNOW THE DATA based on information in the protocol, the Investigator's Brochure, and any other available source. Explain that since this is research, part of the objective of the study is to better determine the likelihood of these risks as well as unidentified risks. Explain how risks will be minimized by medical screening and careful monitoring.
- CHOOSE YOUR WORDS CAREFULLY. Although it is necessary to inform subjects of the risks of study participation, measure your responses so that you are not unnecessarily alarming subjects.
- Explain OTHER BENEFITS of participating in a clinical trial:
  - Benefit to mankind, benefit to others.
  - Contribution to science, on the cutting edge of research, being a part of history.
  - Free health care and health monitoring.
  - Priority in office visits.
  - Improved personal health.
  - Opportunity to learn more about the disease.
  - Compensation, if applicable.
- At least TWO COPIES of the Informed Consent Form must be presented to the subject—one for the study files that is signed by the subject/witness/guardian and one for the subject to keep as a record and reference. A third signed copy may be required for the medical record.
- Emphasize to subjects that participation is VOLUNTARY and that they may withdraw at any time. Assure them that you are their ally, regardless of their decision to participate in the study.

ASSESSING SUBJECTS FOR STUDY PARTICIPATION

The first step in assessing subjects may occur before they come to the clinic. Review all available medical records and recent lab results to determine patients who may be eligible for the trial. If screening requirements in the protocol are considerable, you may want to establish a prescreening visit, keying in on select criteria (e.g., key variable determinant of disease) to assess eligibility quickly before investing more time and money in the subject.

When assessing subjects, it is important to get accurate information. Enrolling ineligible subjects is to no one's advantage and may even endanger the subject. The first step in the screening process is to review the inclusion and exclusion criteria for the study. The potential subject should meet all of these criteria without exception. Often, a subject is "close" to meeting the criteria, and there may be a request to "relax" the criteria to enroll the subject. Remember to think of all the possible ramifications: Are you putting the subject in danger? Will the subject be unevaluable at the end of the trial? Is this a protocol violation?

It is not enough to simply read the inclusion/exclusion criteria items to the subject and check off the response. You must interview the subject and PROBE to assure that he/she understands the questions and is giving you accurate responses. You need to ask the right questions in order to elicit accurate responses. For example, you may ask the patient if he/she has taken any medication in the last week and be told "no." However, on the medical history form you see that he/she had a headache for three days last week. You would want to investigate further to see if any medication had been taken for the episodes of headache.

There are ways to determine if the subject is providing accurate responses:

- Review previous medical records (be sure they are up to date).
- Have the subject complete a new medical history form and compare it to previous records.
- Do relational checks: The subject has a chronic illness but reports no medications; the subject reports symptoms indicative of an chronic illness; the subject reports hospitalizations but no surgeries. Use all of the information available to you.
- Question the subject IN DEPTH about responses. If something does not appear right, probe further.

Additionally, the CRC must try to judge the *character* of subjects—are they reliable? truthful? Are they motivated to participate in the study? Are they intelligent enough to follow study requirements? What are their motives for being in the study? Formal personality (psychological) assessments are acceptable as long as informed consent is obtained.

Assessment tools may be very useful in screening subjects. Medical history forms or special forms/questionnaires that you develop for the study may be useful. It may even be desirable to perform personality assessments (especially if the investigational agent is a narcotic).

KEEPING THE SUBJECT ON THE STUDY/ FACILITATING COMPLIANCE

Now that you have identified subjects and enrolled them in the study, your next task is to KEEP THEM ON THE STUDY and to assure their COMPLIANCE with the study requirements. There are many potential problem areas, and the CRC must anticipate these problems and proactively avoid them.

Study Design

The design of the study alone will determine how eager subjects are to be in the study. Things that will make participation more attractive and increase compliance:

- Length of the study: studies of shorter duration.
- Number and frequency of study visits or assessments.
- In-house (or clinic visit) dosing.
- Less frequent dosing (qd vs. qid).
- In-house versus outpatient treatments (it is easier to keep patients compliant with in-house treatments; with outpatient treatment, it is more convenient for the patient but variable).
- Expertise of the research team.
- Ability of the research team to maintain control over the study (e.g., study conducted in a specialized clinical research unit as opposed to a hospital ward or through the emergency room [ER]).

Study Visits

Potential problems include missed visits, subject has not allotted enough time for all of the visit tests, waiting to be seen takes too long/wastes subjects time, and parking is difficult/costly.

To avoid problems:

- Provide the patient with a copy of the study schedule of events that details specific assessments done at each visit with an estimate of time involved.
- Create a subject-specific calendar for the subject that indicates scheduled visits by day, time, and expected length of visit.

- Use return appointment cards. Use postcard reminders or phone call reminders of appointments.
- Give priority to study subjects in the clinic waiting area—highlight appointment cards with "study subject"; highlight in appointment book.
- Hold specific clinics for study subjects only.
- Be prepared for the study visit: have the subject's chart and all necessary forms/completed lab requisitions ready ahead of time.
- Have a schedule for the day to give to the subject, e.g.,

Clinical labs	2nd floor	room 212	9:00 A.M.
X-ray	1st floor	room 109	9:30 A.M.
CRC	clinic	room 205	10:00 A.M.
PI	clinic	room 205	10:30 A.M.

- Verify all appointments with other departments, e.g., labs, X-ray, and so on.
- Arrange for shorter visits with less critical procedures (e.g., clinical lab draw only) to be conducted at satellite clinics closer to the subject or through the subject's private physician.
- Be flexible when you can, and without compromising the study, about rescheduling visits. Try to "salvage" subjects who miss a scheduled visit.

FOLLOW UP IMMEDIATELY ON ALL MISSED APPOINTMENTS.

Parking

Pay for parking for study visits; get parking passes; try to get preferred parking areas for subjects.

Subject Characteristics

The selection of the subject alone may be a measure of compliance. Factors include the following:

- What is the disease and state of the disease for the subject? A sicker subject may be more likely to comply.
- What are the CONSEQUENCES of noncompliance? How serious is it to the subject's health and well-being?
- Does the subject fully understand the study and the informed consent process? Will the subject feel betrayed later if he/she misunderstood any part of the study?

Generally, you would want to exclude or at least reevaluate the following types of potential subjects:

- Substance abusers.
- Transients (people who are likely to move away before completion of the study).
- People traveling a great distance to participate in the study.
- Serious or severe concomitant illness/disease.
- Medication for chronic disease.
- Debilitating diseases.

Additional Ways to Enlist Compliance

- Urge subjects to CONTACT you if they have any questions or problems. Return calls as soon as possible and provide subjects with your beeper number.
- Use PATIENT DIARIES. The diary is considered a part of the source document if it is specifically required by the study. Note that it is not always necessary to have the diary as part of the patient's medical record or part of the Case Report Form when it consists only of informal notes kept by the subject. Diaries may include notes regarding side effects, taking the medication, concomitant medication, diet, and so on. They may be used for review by the CRC to determine if the patient has been compliant in study requirements. For example, the patient may mark the time medicine was taken, note dietary intake, and list adverse events.
- PACKAGE the investigational agent so that it is easy for the subject to keep track of dosing. Blister packaging is very useful in this way (see Chapter 9).

- Provide the subject with written detailed INSTRUCTIONS, especially for taking the investigational agent (see example in Chapter 9).
- Maintain close contact with the subject and provide MORAL SUPPORT.
- The CRC and investigative staff should be ENTHUSIASTIC about the study—make it contagious, motivate the subject to be excited about the study.
- ENCOURAGE the subject along the way—e.g., "Great, you've made it to the halfway point!"
- Give the subject SPECIAL CONSIDERATION—a good subject in this trial may be considered for future trials.
- Show an INTEREST in the subject—ask about family, note special occasions.
- Provide the subject or his/her private physician with RESULTS of their assessments.
- Involve the subject's FAMILY/FRIENDS and enlist their support.
- EDUCATE the subject about the disease and/or the study process to raise interest in the study.
- Provide some CONTINUITY of care—try to have consistency in the staff evaluating the subject from visit to visit.
- Have FLEXIBLE SCHEDULING—see subjects in the evening, on weekends, or at-home visits. If subjects must travel a great distance, try to arrange monitoring through telephone contact and/or visits to their private/local physician.
- Prepare a brochure of INFORMATION for the subject. Include appropriate phone numbers, maps, and so on. Design a section to record all scheduled study visits.
- Establish a CONTRACT with the subject. For example, with a known alcohol user, provide in a contract that if the subject abuses alcoholic substances during the trial, he/she will be terminated from the study without further compensation.

- Include mechanisms for SCREENING for subject compliance (drug screens, special lab tests, evaluation of key clinical labs).

WHEN NONCOMPLIANCE IS NOTED, CORRECT THE SITUATION AS SOON AS POSSIBLE.

DETERMINE IF THE SUBJECT CAN CONTINUE THE STUDY. Does the violation invalidate the subject's data? Will the subject continue to be noncompliant, and would it be better to cut your losses early?

DETERMINING NONCOMPLIANCE

Responsibility for determining and assessing noncompliance may vary. It could be the CRC or subinvestigator. It is recommended to involve the investigator and possibly the sponsor in cases of noncompliance. Other than obvious methods of determining noncompliance, e.g., observation, missed visits, failure to return to the clinic, a few other methods may be used to assess compliance:

Investigational Agent Inventory (pill counts)

In outpatient studies, assess the amount of investigational agent returned. Does it match with what was prescribed? Note that this is not foolproof—subjects are very good at figuring out what they need to return.

Lab Values

By evaluating scheduled and *nonscheduled* clinical lab values, you may be able to pick up changes in lab values indicative of noncompliance.

Drug Screens (urine or blood)

If substance abuse is suspected, analyze for drug levels or metabolites in urine or blood samples. Here are some specific recommendations (4):

1. Use CAGE questionnaire to screen for alcohol abuse.
2. Use a breath analyzer for detection of alcohol at screen and randomly during a study.
3. Adequately document use of over-the-counter and prescription medication at screen and during a study.

4. Perform urine drug screens on all subjects and repeat at random intervals during a study.

Keep in mind that a discussion of random screens should be included in the informed consent process.

Patient Diaries Review subject diaries for contradictory information.

Interview Subjects Ask probing questions to determine if subject was compliant. Insist on details.

SUBJECTS LEAVING THE STUDY

Despite attempts by the CRC and PI to keep the subject compliant and on the study, a significant number of subjects will leave the study for a variety of reasons:

- Subject chooses to discontinue.
- The investigator chooses to discontinue the subject.
- Subject experiences an adverse reaction preventing him/her from continued participation.
- Subject does not respond to treatment and may require other treatment (although this may be an endpoint for the study).
- Subject develops an intercurrent illness preventing him/her from continued participation.
- Subject is removed from study for noncompliance.
- Subject is removed from study because of a protocol violation.
- Subject fails to return to clinic despite numerous attempts and therefore is lost to follow-up.
- Subject is moving to another town (if this is a multicenter trial, the subject may be able to continue at another site).
- Subject dies.

A subject may discontinue for a combination of these reasons. However, for purposes of data interpretation, it is necessary for the CRC and PI to determine the single, most significant reason.

WHAT IS AN EVALUABLE SUBJECT?

Generally, subjects are evaluated for two categories: safety and efficacy. ANY SUBJECT WHO HAS RECEIVED AN INVESTIGATIONAL AGENT IS EVALUATED FOR SAFETY; that is, if the patient has taken the investigational agent, he/she may have experienced adverse effects that are significant to the drug safety profile and must be considered in analysis. Often, even subjects who have been enrolled in a trial but have not received any drug, e.g., involved in a washout period predosing, will be evaluated statistically on an "intent to treat" basis.

The rules for evaluating subjects for efficacy are quite different. THE GUIDELINES FOR DETERMINING EFFICACY ARE OUTLINED IN THE PROTOCOL. In almost all cases, it is necessary for the subject to complete the study (i.e., reach a study-defined clinical endpoint or complete a specified time period) to be considered evaluable for efficacy analysis. The protocol should outline specifics for defining an evaluable subject, especially in crossover studies.

Keep in mind that what is considered to be an evaluable subject may have implications on financial reimbursement.

SUBJECT COMPENSATION

If subject compensation is part of the study plan, the CRC and PI will have to determine a mechanism for payment to subjects. Note that subject compensation must be reviewed by the IRB to determine if it is appropriate. It may be necessary to establish a separate account for payment to subjects, or it may be necessary to administer funds through a study grant and/or through the institution's administration (good luck!). Have a plan in place so that subjects can be compensated quickly and with little hassle.

Ideally, if the compensation is considerable, a portion should be paid to the subject upon enrollment (mostly to cover expenses), possibly with interim payments if the study is very long. A portion of the payment should be given after the subject has met all of the study participation requirements. The compensation schedule must be carefully developed so that it is not coercive.

Compensation should be contingent on the subject's compliance with study requirements. Make this known to the subject from the outset. Additionally, it is wise to have a contract agreement with the subject outlining what the compensation will be and what, specifically, is required of the subject to be eligible for compensation. Clearly

state terms that will terminate the subject's participation and invalidate the terms of compensation.

SUBJECTS AND THE MEDICAL TEAM RELATIONSHIP

We must always remember that the patient/subject should be the first consideration whether in a clinical study or as a patient in the clinic or hospital. Dr. Patty Zekan, an oncologist involved in patient care and clinical trials, has developed a "Bill of Rights" (based on *A Patient's Bill of Rights* originally developed by the American Hospital Association in 1973) as it pertains to cancer patients, healthcare workers, and the patient's family. These concepts certainly apply to the clinical research setting. It is important to note that the patient, healthcare professional, and family not only have rights but also responsibilities in the patient/healthcare team relationship.

THE CANCER PATIENT'S BILL OF RIGHTS

The patient has the right

1. To know the disease; to be informed of all aspects of the disease and treatment.
2. To ask questions, asking only those questions he/she wants an answer to.
3. To choose the type of therapy (or none), sharing in all decisions along the way.
4. To be advised in any experimentation affecting his/her care.
5. To react emotionally; to have and express
   a. feelings of anger.
   b. feelings of fear.
   c. reactions to family including protection/withdrawal/demands.
6. To open communication and honesty.
7. To expect competent, considerate, and respectful medical care.
8. To expect compassion from the medical team.
9. To privacy concerning care and confidentiality of records.
10. To choose the manner of treatment when actively dying.

The patient has the responsibility

1. To communicate openly and honestly with family and health care team, especially if there are concerns he/she feels are not adequately addressed.
2. To provide accurate information regarding past and current health history.
3. To cooperate with care and treatment as long as it is the treatment the patient has agreed upon.
4. To show consideration for the rights of family members, health care team members, and other patients.

THE HEALTH CARE TEAM'S BILL OF RIGHTS

The health care team has the right

1. To have and express feelings
   a. concerning death (fear of mortality, inadequacy, guilt).
   b. of anger.
2. To care.
3. To have coping mechanisms.
4. To expect gratitude.
5. To expect and receive communication—from the patient and from the family (entire team must *communicate* with each other to present a unified treatment plan).
6. To continue his/her education and to be up-to-date.

The health care team has the responsibility

1. To provide expert medical care.
2. To educate family and patient regarding illness and treatment.
3. To relieve symptoms—pain and suffering.
4. To care.
5. To be positive—to give hope.
6. To "Prinum Non Nocere"—"First, do no harm."
7. To be available.

THE FAMILY MEMBERS' BILL OF RIGHTS

The family members have the right

1. To have and express feelings of
   a. guilt.
   b. anger.
   c. denial.
   d. hope.
   e. fear of separation.
2. To acquire knowledge about the patient's disease and condition.
3. To expect support from the health care team.
4. To use coping mechanisms.
5. To expect and receive open and honest communication.
6. To be included in terminal choices.

The family members have the responsibility

1. To communicate.
2. To have respect for the patient's choices.
3. To accept the health care team.
4. To communicate within and among family, and to appoint one spokesperson to communicate with the health care team.
5. To be available.

"The Cancer Patient's Bill of Rights," "The Health Care Team's Bill of Rights," and "The Family Member's Bill of Rights" all reprinted by permission of Dr. Patty Zekan.

Bobbie Atwell, Director, Cancer Patient Support Program at Bowman Gray School of Medicine, has discussed this concept in the article "The Rights of Cancer Patients" in the *Arizona Counseling Journal*, Vol. 10, pp. 67–76, 1985.

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7

DATA MANAGEMENT

Data from clinical trials must be collected, recorded, and reported in a systematic and accurate manner. There are many steps in the data management of clinical trials:

- Developing forms for data collection.
- Collecting the data.
- Accurately recording the data.
- Entering data into the database and assuring the quality of the data.
- Analyzing the data.
- Reporting the data.

The Clinical Research Coordinator (CRC) is key in assuring that the cycle of data collection and reporting runs efficiently.

GENERAL ISSUES IN DEVELOPING FORMS FOR DATA COLLECTION

Data in clinical trials may be collected by a variety of means. Most studies collect data prospectively using data flow sheets or Case Report Forms (CRFs). Data flow sheets are designed to record selected data over time in various columns. The data may be summarized on a separate summary page, or all data may be computerized for analysis. CRFs are generally used by pharmaceutical companies and are often very detailed and complex.

Most studies gather data in the following general areas:

- Demographics (sex, birth date, age, weight, height, race, marital status).
- Patient medical history.
- Diagnosis (primary and secondary, coexisting medical disorders).
- Investigational agent administration (dates, time, identification, and code numbers).

- Other drugs and treatments (previous, concomitant, adjuvant).
- Physical examinations.
- Vital signs (temperature, blood pressure).
- Clinical laboratory (blood chemistry, hematology, urinalysis, other specific tests).
- Adverse reactions.
- Efficacy parameters.
- Study completion.

The CRF should reflect the protocol and be designed to record and document all of the required data. The criteria for CRF development are as follows:

- The CRF relates directly to the parameters of the protocol.
- The CRF is easy to complete, clear and concise, and does not duplicate data.
- The CRF is easy to review.
- The data are compatible with the computer database.
- The CRF does not collect extraneous information not related to the objective of the protocol.

ASSURING DATA ARE COLLECTED

The second step in data management is collecting the data. Data should be collected as CONSISTENTLY as possible. How is this achieved?

- All persons making assessments on patients should agree to the same guidelines. Ideally, the same person should assess the same subject at each visit.
- Use the same clinical laboratory for testing.
- Use study aids (see Table 7.1).
- Develop a rapport with subjects so that they understand their obligations in the study and are willing to return as scheduled.
- Record data directly on the medical record; transcribe to data flow sheet or CRF *as soon as possible*.
- Advise ancillary personnel (e.g., lab technicians) of the study requirements.

TABLE 7.1 STUDY AIDS IN COLLECTING DATA

- Use the protocol schedule of study visits and evaluations (see Appendix D) or study schema.
- Design subject worksheets by visit date and required parameters.
- Design a calendar for each subject with study visits outlined.
- Refer to relevant CRF pages.
- Design visit-specific pages listing required parameters for each visit to attach to the subject's chart during the visit.
- Prepare all paperwork, e.g., clinical lab requisitions, ahead of time.
- Establish a query system or prompt for subject return appointments.
- Keep a calendar of all subject return appointments.

RECORDING DATA AND COMPLETING CASE REPORT FORMS

Accurate recording of data in a clinical trial is a very critical step. Accuracy, legibility, and consistency are key. Recording data on flow sheets or completion of CRFs is a very time-consuming and tedious process. Data entries on CRFs should be completed on a regular basis (ideally, immediately following the subject visit) to avoid a backlog of entries and to ensure that accurate data are captured. Table 7.2 lists guidelines for recording data and completion of CRFs.

Data on CRFs will be reviewed by the monitor and then reviewed again by the data management/data entry group at the sponsor's offices. Table 7.3 presents common areas where data are verified and errors may be detected.

Ultimately, the CRF is a part of the New Drug Application (NDA) and the FDA (U.S. Food and Drug Administration) has access to each CRF for all studies.

TABLE 7.2 GUIDELINES FOR RECORDING DATA AND COMPLETION OF CASE REPORT FORMS

1. Follow directions for completing the CRF and obtaining variables as written in the protocol, study procedures manual, and CRF.
2. Make all entries in black ink to maximize legibility and facilitate copying.
3. Print legibly and neatly.
4. Use acceptable medical terminology.
5. All comments should be brief, concise, clear, and confined to "comment" sections of the CRF. Write comments only if they apply to the study and the topic.
6. Correct errors by drawing a single line through the incorrect entry, reenter the correct data nearby, initial, and date the correction. DO NOT write over data, erase data, or use correction fluid. If data are to be rewritten onto another CRF page, make a note on the original page, line-through the page, initial, and date. If the CRF was signed by the investigator, he/she also must initial the new page verifying agreement with the data.
7. Complete all blanks. If data are missing, use one of the following conventions (verify use with sponsor):
   - NA Not Applicable.
   - ND Not Done.
   - UNK Unknown.

   Do not draw lines to indicate missing data.
8. Verify that items entered in "Other" categories do not fit in a coded field.
9. Verify UNITS and TIME are recorded as specified on CRF.

   (Appendix E contains algorithms for conversions.)
10. Data must be complete for the day, month, and year during the study.
11. When using study-specific rating scales or codes, use only the options provided.
12. Use only CRFs designed for the particular study.
13. Check that all errors and crossouts are initialed.
14. The investigator must review and sign each CRF after completion.

SOURCE DOCUMENTS

Data are recorded from a variety of source documents: clinic notes, medical records, nurse's notes, radiology reports, and lab reports. Even the appointment book and hospital census are considered source documents. The investigator is required to maintain source documents as well as provide specific data for the analysis of the study. Sponsor representatives and FDA inspectors need to have access to subject records. (Permission from the subject should be obtained as part of the informed consent process.) The monitor will verify data entries against source documents for accuracy and content during periodic site visits.

TABLE 7.3 COMMON AREAS FOR VERIFYING SUBJECT DATA

1. Inclusion/exclusion criteria: Were subjects entered appropriately? Verify per source documents (medical record, lab results).
2. Verify entry date to date informed consent signed.
3. Verify all dates to source documents.
4. Especially be aware of transcription errors commonly occurring for patient ID number, initials, dates on each page.
5. Verify all visits according to protocol.
6. Verify birthdate (especially the year).
7. Verify all data (clinical labs, PE, etc.) to source documents.
8. Check adverse events. Review the event, relationship to drug, severity. Do any of the adverse events qualify as serious adverse events requiring an Investigative New Drug (IND) Safety Report to the FDA?
9. Has the Principal Investigator or a registered subinvestigator signed the CRF?
10. Are all boxes completed?
11. There are no missing or incomplete data.
12. Review clinical lab results for indication of adverse events.
13. Investigational agent administration is ACCURATELY recorded, agrees with protocol dosing guidelines, and matches the drug accountability record.
14. If changes are made, assure that all related data are updated accordingly.
15. All corrections are clearly written, initialed, and dated.

Every subject in the trial should have a separate clinic chart/medical record. Minimally, visit dates and clinician's comments should be recorded. Lab reports should be included in the record as well. All investigative and/or clinic staff examining subjects should be very diligent and precise when writing clinic notes.

The following specific items should be recorded:

- Data not reported elsewhere, e.g., temperature, height, weight, blood pressure, physical exam findings.
- Subject's comments suggestive of an adverse experience.
- Any comments suggestive of noncompliance.
- Any irregularities, e.g., missed doses or taking concomitant medication.
- Phone contact with subject.
- Attempts at contacting subjects "lost to follow-up."

Be aware that any discrepancies corrected in the source document might require a correction on the CRF. Similarly, corrected information on the CRF should be supported by source documents.

Healthcare professionals receive specific training in recording information in medical documents. Table 7.4 contains guidelines for medical record documentation.

Source documents must be maintained as long as all other study materials: for a period of two years following the date of NDA approval for marketing for the indication studied, or if no application is filed or one is not approved, until two years after the notification to the FDA that the investigation (IND application) is discontinued (21 CFR 312.62). For studies conducted to meet ICH GCP Guidelines, records must be retained for two years after approval in the last country submitted. Verify that the institution's policy for the retention of medical records meets these requirements. Also, determine the institutional policy for disposition of medical records of deceased subjects. Where are the archives? Are the files readily accessible?

Electronic Data Transfer

Central labs used for clinical trials or individual labs often arrange for transfer of data through computerized methods or by electronic tape. These data transfers are less likely to produce transcription errors (and relieve the CRC of *a lot* of data entries). **However, a hard copy of the lab results must be maintained with the subject's permanent record and CRF.**

Additionally, hospitals and clinics are becoming more sophisticated in the collection of patient data by specific software programs. It *may be* possible to transfer (by disk or modem) selected pieces of patient data to the sponsor electronically, eliminating transcription of data to CRFs. However, as above, it is necessary to maintain hard copies (printouts) of the data with CRFs, and there must also be a way to verify data (source document verification). The investigator also will have to review the data and sign appropriate forms.

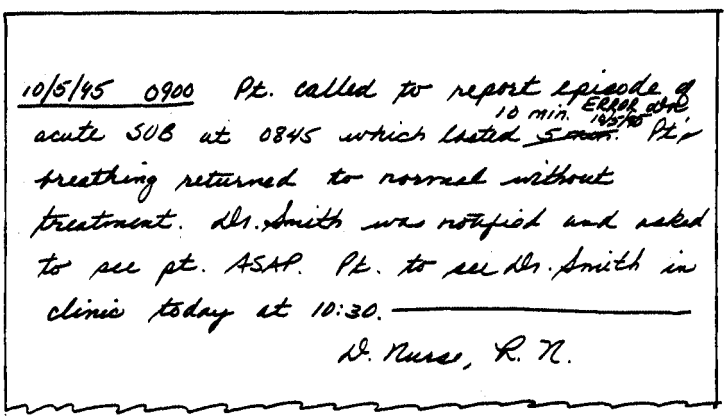
Remote Data Entry

One method of collecting clinical trial data is by remote data entry. A computer terminal is set up at the site and connected to the sponsor's data bank by modem. The purpose is to decrease the time involved in data collection and entry by directly entering the data.

TABLE 7.4 GUIDELINES FOR MEDICAL RECORD DOCUMENTATION

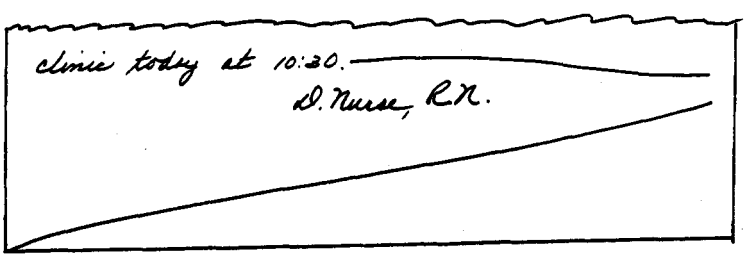
- Write date/time at each entry (military time is preferred or use A.M. or P.M.).
- Write legibly, clearly, neatly.
- Use black ink (reproduces best in case of legal action).
- Cross out errors with a single line, write "error" and correct entry, then initial and date the correction. If there is not enough room, use the next line to make the change.

  Example:



- Make a line through empty space remaining after a note, then sign your name and title.
- If a page portion is skipped (blank), cross a single line through it and begin your note at the next page at the top or at the next available space.

  Example:



- Use proper units of measurement for all entries.
- Never use correction fluid. The old entry should always be visible.
- Never "estimate" data points that are quantitative. If you forgot a data point, write "omitted," or circle and leave blank. Consult with the study sponsor about handling missed data.
- Be sure to receive proper permission before removing parts of the patient chart or copying it.
- Remember that all patient information is strictly *confidential* and constitutes a *legal document.*

The data will be reviewed by the monitor either at the site or electronically, and clarifications may be discussed with or e-mailed to the CRC. Remote data entry systems must have security mechanisms to assure the integrity of the data (21 CFR 11). When using remote data entry, it is imperative to maintain a hard copy of the data at the site.

Maintaining/Storing CRFs

The original copy of the CRF generally goes to the sponsor and is kept at the sponsor's facilities. Some studies will require that copies of the CRF be submitted to the sponsor by fax to facilitate timeliness of data collection. Accurate copies (photocopy or NCR paper) of the CRFs must be kept by the investigator with the study files for the following time periods:

- **Two years following the approval of the NDA**
- **Two years following the discontinuation of the IND application.**

Note that this is *not* two years after your site completes the study. Actually, this can be quite a long time! If your study was an early Phase II trial, it may be five to seven years before enough data are gathered through the completion of the Phase III studies, the writing and submission of an NDA, and review at the FDA.

Also note that electronically submitted clinical lab data and data submitted by remote data entry must be backed up with hard copies in the study file.

ANALYZING THE DATA

Data from CRFs or flow sheets are generally entered into a computer database. A statistician analyzes the data according to the statistical analysis plan stated in the protocol. Queries may be generated during this process, and the monitor will discuss them with the CRC and investigator. The data are summarized into tables and statistical figures for inclusion in the final study report and submission to the FDA in an NDA.

REPORTING THE DATA

Data from clinical trials are reported in final study reports. Each investigator must summarize the events of the trial at that particular site with his/her patient population and submit the report to the Institutional Review Board (IRB) and the sponsor of the trial. This report should include the following:

- Dates of the beginning and end of the study.
- Number of subjects enrolled.
- Number of subjects completing the study.
- Number of dropouts and reasons.
- Summary of adverse events.
- Notation of patient deaths, if any.
- Overall opinion of the effect of the investigational agent.
- Comparison with other effective treatments.
- Summary and interpretation of clinical laboratory values outside of the normal range.
- Listing of protocol violations and explanation.
- Discussion of any specific subject experiences, if warranted.

Additionally, the investigator may wish to publish the results with the approval of the sponsor.

In the bigger picture, the sponsor will summarize all of the data from all trial sites and prepare a final study report or final medical report. This report is a detailed summary of the statistical and clinical results of the trial. Emphasis is placed on the safety and efficacy of the investigational agent. Generally, a discussion is included that positions the investigational agent as an effective treatment in the disease being studied. The report may be part of an NDA, a line extension, an OTC conversion, marketing, or for publication in medical journals.

REGULATORY REFERENCES

21 CFR 312.62.
21 CFR 11.

Guidelines

Recordkeeping in Clinical Investigations (10/95).

Compliance Program Guidance Manual (Clinical Investigators) (8/18/94).

Guide for Detecting Fraud in Bioresearch Monitoring Inspections (4/93).

See also references for site inspections.

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Data Collection Forms in Clinical Trials. B. Spilker, Raven Press, New York, 1991.

Designing Case Record Forms for the World Wide Web. Paul Bleicher, Richard Dab, Patricia Giencke, and Jeffrey Klofft, *Applied Clinical Trials,* Vol. 7 (11), p. 36, 1998.

Drug Information Journal, Vol. 28 (2), 1994. Contains multiple articles on the following topics:

- Clinical Laboratory Data: Practical Approaches to Using Control Laboratories in Error.
- Clinical Safety Data Management in Japan.

Electronic Exchange of Laboratory Data: Recommendations for Improving Quality and Reducing the Hidden Costs. PMA Task Force, *Drug Information Journal,* Vol. 27 (3), 1993.

Identify Yourself! Computer Security and Authentication. Paul Bleicher, *Applied Clinical Trials,* Vol. 8 (10), p. 40, 1999.

Sign Here Please, Mr. Bond. Paul Bleicher, *Applied Clinical Trials,* Vol. 9 (8), p. 28, 2000.

8

ADVERSE EVENTS

One of the major objectives of clinical trials is to assess the safety of experimental agents. This is primarily done by determining and tabulating "adverse experiences" (a.k.a., adverse events, adverse drug reactions, side effects). Clinical adverse experiences (AEs) are adverse events and/or symptoms that develop during the clinical trial.

Serious, unexpected adverse events require prompt reporting to the U.S. Food and Drug Administration (FDA) via an Investigative New Drug (IND) Safety Report. Most subject deaths fall into this category as well. The clinical research team is responsible for recognizing, treating, and reporting all adverse events occurring to subjects in clinical trials.

ADVERSE EVENTS

The FDA requires reporting of adverse events of investigational agents to assure subject safety. The pharmaceutical sponsor who is dependent on reports from the investigative site generates these reports. Most common adverse events are collected on the Case Report Form (CRF) and submitted to the sponsor for inclusion in the New Drug Application (NDA) and ultimately the package labeling. For those adverse events defined as "serious and unexpected," the FDA accepts narrative reports but prefers reports submitted on a MedWatch form. They will also accept reports on a CIOMS form, which is the form used in many international studies and recognized by the International Conference on Harmonisation (ICH). These reporting requirements are discussed later in this chapter.

The NCI has adopted a system called AdEERS (Adverse Event Expedited Reporting System) as a Web-based system designed to allow cooperative groups, cancer centers, and single institutions to submit expedited reports for serious and or unexpected events to the NCI for all trials using NCI–sponsored investigational agents.

Table 8.1 provides definitions of adverse events/adverse experiences as defined by different regulatory agencies.

TABLE 8.1 DEFINITIONS OF ADVERSE EVENTS

Source	Terminology	Definition
21 CFR 310.305 (21 CFR 312.32 for discussion of serious adverse events)	Adverse Drug Experience	"Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action." The FDA defines both serious and life-threatening adverse drug experiences in 21 CFR 312.32.
ICH GCP	Adverse Drug Reaction	". . . all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. . . ."
ICH GCP	Adverse Event	"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."
NIH Guidelines, 1/01	Adverse Event	Any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment procedure (attribution of unrelated, unlikely, possible, probable, or definite).
OHSR Information Sheet #17	Adverse Event	Any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome, or disease that either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen.

ASSESSMENT OF ADVERSE EVENTS

The medical team is usually second to hear about an adverse event; the first, of course, being the subject. Once something is recognized as out of the ordinary and possibly an

adverse event, a detailed assessment must be performed. Some ways this is done are as follows:

- Review of clinical lab results.
- Subjective reports from subjects.
- Observation/physical exam by research team.
- Questioning (AE probe) by research team.

The techniques used in gathering adverse event information are critical to the validity of the event.

CLINICAL LAB RESULTS are generally reliable, especially when accompanied by clinical signs and symptoms. However, it is always best to verify an abnormal lab result by a repeat sample to ascertain accuracy. This is especially true when the action taken by the medical team would be to discontinue the investigational agent, modify the dose, administer a nonprotocol-approved concurrent treatment, or would result in the subject's being discontinued from the study.

SUBJECTIVE REPORTS of adverse events from subjects must be assessed by the medical research team and not taken verbatim from the subject. For example, the subject reports a "severe" headache. Ask questions to determine if the headache is "severe" by protocol criteria.

When requesting adverse event information from the subject, be careful not to "lead" the subject. You may want to ask open-ended questions, e.g., "Have you had any problems you want to tell me about?" or "How have you been feeling since your last visit?" Sometimes the sponsor may request that a list (AE probe) of specific symptoms be read to the subject to determine signs, symptoms, or adverse events.

The research team often will OBSERVE adverse events, particularly in an in-house setting. Observations may be direct, such as observing a subject walking unsteadily, or they may be from specific monitoring equipment, such as an electrocardiogram (ECG).

In all cases, the Clinical Research Coordinator (CRC) should ask appropriate questions to collect accurate data on subject adverse events. Reports of AEs and the details should be documented in the subject's clinic chart/medical record as well as reported on the CRF.

Remain as OBJECTIVE as possible while collecting study data and handling adverse events. The clinical trial is not a contest between the study sponsor (pharmaceutical company) and a given patient population; one party is not the "good guy" and the other the "bad guy." As a healthcare provider, you are naturally the subject's advocate, and you

should fulfill that role as you deem appropriate. Be careful not to suggest to a subject that he/she is on active drug because he/she is reporting a specific side effect or let a subject "skip" certain diagnostic tests required by the study because you or the subject feel the testing is excessive. Discuss your concerns with the investigator and sponsor representative. Changes can be made along the way, when appropriate. Separate yourself from the subject and the sponsor so that you can facilitate a fair, objective, safe study.

Once an AE is identified, obtain complete detailed information about the occurrence and then characterize it:

Dates	The date of onset and cessation should be accurately recorded.
Severity	Mild, moderate, severe, or "graded" numerically according to a toxicity grading scale provided in the protocol.
Relationship to Drug	Was the event associated with the use of the test agent? Options are usually yes/no or definitely/probably/possibly/remotely related.
Treatment	Was treatment required? What was the treatment/action?
Outcome	Did the subject recover from the AE?
Seriousness	This category relates specifically to reporting requirements to the sponsor and the FDA and is covered in detail on page 152.
Unexpected	Relates to reporting requirements to the sponsor and FDA and is covered in detail on page 152.

AE data from clinical trials are compiled and submitted to the FDA as part of the NDA and/or as an annual report to update the IND. The information is CRITICAL to the decision to market the investigational agent—the investigational agent must be safe but its safety (risk) must be weighed in comparison to the efficacy (benefit) of the drug, referred to as the RISK/BENEFIT RATIO. The information reported through AE data collection becomes the basis for the package insert to be used for the marketed agent.

RECORDING ADVERSE EVENT DATA

AEs are recorded in the CRF or on the data flow sheet. It also is imperative that the information about the AE be recorded in the subject's clinic chart or medical record. The information should not be contradictory. If new information is added outside a clinic visit (e.g., phone call from subject, visit to the emergency room), make sure the information becomes a part of the subject's permanent record. This is important for three reasons:

1. The subject's permanent record needs to be complete for the optimal medical care of the subject.
2. The sponsor and the FDA will use the medical record as source documentation to verify data in the CRF.
3. It is required for validation of data during a quality assurance audit or FDA inspection.

When recording AEs, be concise and use common, accurate medical terms. Most AE data are converted in the database to a classification system, e.g., the COSTART or WHO classification system, to allow for grouping of AEs by body system and for data analysis. Therefore, it is necessary to avoid being ambiguous so that the AE is accurately coded.

Identifying AEs is not always easy. Although you want to record all potential AEs, you need to do some exploration to further characterize the AE. Some factors to consider are as follows:

- Is the AE a known side effect of the investigational agent as defined in the current Investigator's Brochure or protocol?
- Is the AE likely to be related to the disease state of the subject—is it a known symptom of the disease?
- Are there characteristics of the subject's medical history or lifestyle that may account for the event, e.g., alcoholism causing abnormal LFTs (liver function tests)?
- Was the AE present at the beginning of the trial and has it increased in severity or disappeared and reappeared during the trial?

It is often difficult to know if symptoms of a disease or just the disease should be listed in the AE data (e.g., runny nose, headache, achy vs. cold). The sponsor should provide guidelines on which convention to use: disease only or list all symptoms, but both symptoms and disease should not be recorded.

The DATES OF ONSET AND CESSATION should be recorded as accurately as possible. If the subject reports that he/she had a headache last Tuesday through Thursday, then those are the dates to record, not the date of the study visit.

It would be useful to ask subjects to keep diaries of their symptoms or to make informal notes to be reviewed by the CRC during the study visit. This information gives the CRC the opportunity to PROBE into the events. Using the headache example above, questions the CRC might ask are as follows:

- Did you take any medication for the headache? (Enter as concomitant medication.)
- What other symptoms did you have?
- Did anyone else you came in contact with have these symptoms?
- How was your big birthday party bash Monday night?

Even if the AE is attributed to something else, e.g., the flu or a hangover, the CRC will still need to record it as an AE. However, the causality would not be related to the investigational agent.

The SEVERITY of the AE should be rated according to the toxicity grading scale in the protocol or, if a scale is not provided or the AE is not on the scale, by medical judgment of the Principal Investigator (PI). The Common Toxicity Criteria (CTC) used by the NIH can be found at http://ctep.info.nih.gov. For example, the subject reports that he had a severe headache. Upon questioning, the subject states that he took one Tylenol® every six to eight hours and felt better. The toxicity grading scale gives the following information:

Grade 1	Mild, no therapy required.
Grade 2	Transient, moderate; treatment required.
Grade 3	Severe, responds to narcotic therapy.
Grade 4	Intractable, requires repeated narcotic therapy.

The AE should be rated as a Grade 2 rather than a Grade 3 (severe) as reported by the subject.

The CAUSALITY of the AE should also be determined with similar questioning and probing. Questions to ask include the following:

- Is it a KNOWN REACTION of the drug? Are there previous reports documenting this type of event with this drug or this class of drugs? Is the event similar to other AEs currently listed for the investigational agent? For example, if anemia

is listed as an AE, other hematological AEs may be likely. Is the event similar to AEs listed for the same drug class as the investigational agent?

- Was the AE reasonably TEMPORALLY RELATED to the administration of the test agent? Consider the half-life and elimination pattern of the investigational agent as well as the clinical context of the event. For example, anaphylaxis occurs immediately after administration whereas anemia or hepatoxicity may take longer to develop.
- Did the AE improve or disappear when the investigational agent was DISCONTINUED?
- Did the AE reappear upon RECHALLENGE with the investigational agent?
- Can the AE be reasonably explained by the subject's CLINICAL DISEASE STATUS? Is the AE more likely to be attributed to the disease or the investigational agent? Are there any other potential causes for the AE?
- What CONCURRENT MEDICATIONS is the subject taking? Can the AE be a result of that medication or an interaction of medications?
- Was the AE present at the BASELINE ASSESSMENT or in the subject's recent medical history? Did it improve and then become more severe with the test agent?
- If the AE was detected by a clinical lab test, verify those results with a repeat sample as soon as possible, especially if the subject has no clinical signs or symptoms. A repeat test may reveal a lab error.
- Is there an abnormally high level of the drug in the serum?

If it is unknown or not clear whether the AE is due to the investigational agent, then it is preferable to err on the side of safety and record the AE as drug related. Often, AEs may be classified as DEFINITE, PROBABLE, POSSIBLE, UNLIKELY, or UNRELATED to the test agent.

- DEFINITE—The adverse event *is clearly related* to the investigational agent(s).
- PROBABLE—The adverse event *is likely related* to the investigational agent(s).
- POSSIBLE—The adverse event *may be related* to the investigational agent(s).
- UNLIKELY—The adverse event is *doubtfully related* to the investigational agent(s).
- UNRELATED—The adverse event is *clearly* NOT *related* to the investigational agent(s).

(NIH Guidelines, January 2001)

MEDICAL MANAGEMENT OF ADVERSE EVENTS

From a practical standpoint, the occurrence of an AE in a study subject may make you feel either slightly concerned or quite alarmed, depending on the situation. The subject who experiences mild nausea for one hour after ingesting his once-a-day study medication is not as worrisome as the subject whose hemoglobin drops precipitously over a period of one week on the study drug, requiring a blood transfusion. The first case involves a mild event that does not greatly threaten the subject's health or lifestyle; the second case is serious and could be life-threatening if not treated immediately. Is the AE associated with the study drug? Should you take the subject off the study drug or modify the dose?

Before taking medical action, try to take a quick look at the whole picture, paying particular attention to (1) the severity of the AE, (2) the AE in the context of the study patient or patient population, and (3) other factors that can have an impact on the subject's well-being while on the study.

Severity of the Event

Patient safety always comes first. When a serious or life-threatening event occurs to a subject in the study, do not let the protocol interfere with the subject's safety. You should

- treat the subject swiftly and appropriately, after lab values have been verified and the subject has been examined thoroughly;
- hold any further doses of study drug until otherwise instructed;
- notify the sponsor; and
- explain as much as possible to the subject to keep him/her informed.

Whenever possible, **work within the guidelines of the protocol** as the AE occurs and is treated. This is where memorization and understanding of the protocol is critical. The CRC who knows the protocol can help the PI make instant medical decisions about subject treatment without compromising the existing study data for that subject. Remember to stay in constant contact with the pharmaceutical sponsor as the AE is reported and treated; you will receive guidance from the sponsor as well.

If the AE is not life threatening or serious, take the time to collect as many details as possible from the subject and make an appropriate decision about continued participation per protocol guidelines. Do not stop study drug administration unless the protocol guides you to do so. If a situation does not fit protocol specifications, and it is unclear how to proceed, consult the study sponsor to discuss the problem. Again, patient safety and well-being come first.

Consider the Subject/Subject Population

Now that the subject's AE has been treated, it is time to review the records and play detective. Why did the AE occur in this subject? Was there prior history of similar events in the subject? For example,

> A subject who calls you reporting an excruciating headache on day three of study drug will cause you concern, but when you see a history of approximately one to two migraine headaches per month in that patient's chart, you may find that this event is, indeed, a typical monthly migraine for that subject. You would ask if there are any differences in duration or intensity from his/her previous headaches.

Next, retrace the study drug's path as it was handled and eventually administered in this particular subject, especially if the drug was self-administered by the subject. Was it prepared properly (mixing required, etc.) and stored properly (specific temperature, restrictions to light exposure, etc.)? Did the subject meet all of the protocol criteria? Did the subject use the correct dose and route? Was the subject reliable in self-administration of the study drug? Check the pill count (or returned vials, tubes, etc.) and review the directions for study drug administration with the subject.

If you have established a fair and trusting relationship with the study subjects during the study, you will have a better understanding of each subject and how the AE fits into the whole picture. You may be surprised sometimes at what subjects may confide. For example,

> In blinded, placebo-controlled studies involving AIDS treatment, a few study subjects were so determined to get at least some active drug (they had a chance of getting active or placebo), that they either had the study drug analyzed at a lab, traded drug with other study subjects, or pretended to take the study drug but never ingested one pill during the whole study (to receive free medical monitoring). The CRCs were able to find out what was happening in each of these cases from conversations with subjects and good observation skills.

Also, keep in mind the subject population when analyzing an AE. Certain symptoms of the disease and expected AEs are often similar. Carefully examine each instance of an AE and determine if the cause should be attributable to the disease or the study drug.

Other Factors Influencing the Subject's Health

Consider other influences outside the study that can have an impact on the subject's health, such as other medications taken before or during the study, environmental exposures (chemicals, foods, etc.), and the psychological impact of illness and treatments. Remember that anxiety can trigger "attacks" whose symptoms mimic many other illnesses—anxiety can be associated with hives, tachycardia, headache, nausea, vomiting, sweating, dry mouth, indigestion, diarrhea, constipation, loss of appetite, weight loss or weight gain, mouth ulcers, shortness of breath, chest heaviness, and so on. Depression is another widely existing condition, especially in chronic-illness populations, that can be confused with AEs.

In summary, if you remember to put subject safety first, work within the protocol as much as possible. By taking time to evaluate the whole picture for each subject's AE, you should be able to conduct a safe, accurate study. Table 8.2 summarizes steps to take in the management of AEs.

TABLE 8.2 STEPS TO TAKE IN THE MANAGEMENT OF ADVERSE EVENTS

1. Stabilize the subject according to standard medical care. The clinical investigator is usually a physician and will make the appropriate medical decisions to treat the subject. If the event is serious or life threatening, consider discontinuing the investigational agent immediately.
2. Run appropriate tests to determine the subject's health status. This includes clinical labs, ECGs, X-rays, etc.
3. If the AE was detected through laboratory tests, take a repeat sample and test within 24 hours to verify the abnormal result.
4. Consult the protocol and study sponsor on the recommendations for handling the situation. Can the subject continue on the study, e.g., with a dose modification or a follow-up phase?
5. Gather information surrounding the event to determine if it was study related or something else unrelated to the study.
6. If the subject must be discontinued from the study, perform all off-study evaluations and continue to follow the subject until the AE abates or returns to baseline.
7. If the event was unexpected, serious, and/or life threatening, notify the sponsor to determine if an IND Safety Report must be filed. Notify the IRB.

UNBLINDING THE STUDY BECAUSE OF AN ADVERSE EVENT

CRSs, PIs, research pharmacists, and study subjects often ask if, under certain circumstances, the study code identifying the study treatment can be broken, thus unblinding the study. This is especially true in the case of an AE. The sponsor of the trial will strongly discourage breaking the code for various reasons.

First, in many subject emergencies that would cause a subject to be discontinued from the study, cessation of study drug is sufficient for further emergency care of the subject. The identity of the study drug would not change the course of the subject's treatment in most cases. In the rare instance where establishing the identity of the study drug is vital for safe emergency treatment of the subject, the investigator would have the authority to ask a third party (usually the pharmacist, who should have access to the code) to unblind the code FOR THAT SUBJECT ONLY (see also Chapter 9).

The second reason for discouraging code-breaking is that, statistically, breaking the code may dramatically reduce the significance or power of the data. The effect on the study would vary according to the study design and the reason for breaking the code.

The third reason is that code breaking raises a "red flag" to FDA inspectors and is a cause for further investigation of fraud by the site or sponsor. To assure that an explanation for breaking the code will be readily available, write a detailed memo to the file as it occurs.

SERIOUS ADVERSE EVENTS: EXPEDITED REPORTING

All AEs occurring during a clinical trial are recorded and analyzed as part of the study. AEs will be reported to the FDA as annual updates to an IND (which include tabulations of AEs) and are submitted as part of the NDA. However, some AEs require reporting to the FDA in a specified time frame. These are SERIOUS and UNEXPECTED AEs associated with the use of the study drug (but limited to those reasonably considered to be drug related). The NCI reporting system is referred to as AdEERS (Adverse Event Expedited Reporting Systems). For investigational agents, the guidelines are specified in 21 CFR 312.32 (see Appendix A). Table 8.3 lists different reporting forms for expedited reporting.

TABLE 8.3 REPORTING FORMS FROM ADVERSE EVENTS AND CONTACT INFORMATION

Reporting Form	Use	Source
MedWatch Voluntary FDA Form 3500 Mandatory FDA Form 3500A	FDA Used for reporting adverse events in clinical trials as well as voluntary reporting of approved products	http://www.fda.gov/medwatch/
VAERS Vaccine Adverse Event Reporting System	FDA Reporting adverse events occurring with the use of vaccines	1-800-822-7967
CIOMS Council for International Organizations of Medical Sciences	International filings	
AdEERS	NCI Reporting of adverse events occurring in NCI and other cooperative group studies	http://cancertrials.nci.nih.gov

Serious is defined as "any experience that suggests a significant hazard, contraindication, side effect, or precaution." This includes any experience that is

- fatal or life-threatening (The patient was at immediate risk of death or death from the reaction as it occurred. This does not include a reaction that, had it occurred in a more serious form, might have caused death.);
- a persistent or significant disability;
- requires hospitalization or prolongs hospitalization; and/or
- a treatment-emergent congenital anomaly.

Note that "severe" is not necessarily a "serious" AE. Severe is a measure of intensity and may be expected as indicated in the Investigator's Brochure and may not be serious. The two terms are not interchangeable.

Unexpected refers to any AE the specificity or severity of which is not consistent with the current Investigator's Brochure or described elsewhere in the risk information in the general investigational plan (i.e., the protocol) or elsewhere in the current application.

Associated with means that there is a reasonable possibility that the experience may have been caused by the drug.

Serious Adverse Experiences (SAEs) must be reported to the FDA. The thrust of the regulations is to increase timeliness in the collection, analysis, and reporting of AEs. The regulations also stipulate that all investigators using the investigational agent are alerted to the SAE. Sponsors of clinical trials generally require that the investigator report the SAE to the sponsor, and the sponsor will report the information to the FDA.

Table 8.4 is a worksheet that can be used in collecting data on an SAE.

Steps in Reporting Serious Adverse Events

1. **Immediately.** Determine that the AE is a reportable SAE (any one of the following will qualify an AE as reportable):
   - Not previously reported in risk information.
   - Is serious as defined in 21 CFR 312.32.
   - Is life threatening.
   - Subject death (almost all deaths must be reported).
2. **Immediately.** Notify the sponsor by phone. Notify the sponsor of the trial immediately if a subject experiences an SAE. Because of the sponsor's history with the investigational agent, the sponsor may have additional information or similar experiences to guide in the management of the subject.

   As indicated in Table 8.5, reports of SAEs must be submitted to the FDA in either a 7-day or 15-day report. Time is of the essence!

   The sponsor may ask additional questions to ascertain all of the pertinent information regarding the SAE:
   - What is the SAE?
   - Subject study number, study day.
   - Summary of subject dosing.
   - Symptoms, onset of symptoms.
   - Concurrent medications.
   - Current status.
   - What medical intervention did the subject receive for the SAE?

TABLE 8.4 INFORMATION TO COLLECT FOR A SERIOUS ADVERSE EVENT

Protocol Title _____

Reported by _____

IND Number _____ Investigator Name _____

Investigator Address _____

Date Notified of SAE _____

FDA Contact _____

Date _____ Date FDA Notified by Telephone _____

PATIENT INFORMATION

Patient Initials _____ Identifying Number _____

Age Years _____ Months _____ Days _____ Birthdate _____

Sex _____ Weight _____ Height _____

Primary Diagnosis _____

Study Day _____ Date Entered Study _____

Date of Last Study Medication _____

EVENT

Description of Event:

Onset Date _____ Cessation Date _____ Ongoing _____

Duration _____

Primary Event:

Relevant Medical History Leading Up to Event:

Relevant Tests/Laboratory Data (pathology, clinical labs, autopsy, tissue drug levels) [attach copies]:

Preexisting Medical Conditions and Other Relevant History:

Table 8.4 continued on next page

Table 8.4 continued from previous page

Concomitant Medications:

Name	Dates	Dose	Frequency	Route	Indication

Reason for Reporting AE:

- ☐ Death Date _____
- ☐ Life threatening
- ☐ Hospitalization or Prolonged Because of Event
- ☐ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Damage
- ☐ Other _____

STUDY DRUG INFORMATION

Name and Strength _____

Lot Number _____ Expiration Date _____

Dose, Frequency, and Route _____

Cumulative Dose _____

Any Dose Reduction Because of SAE? _____

Outcome:

Event Abated After Discontinued or Reduced Dose? _____

Event Reappeared After Reintroduction? _____

Administration Dates (list specific dates and doses):

Relationship to Study Drug:

- ☐ Related
- ☐ Possibly
- ☐ Unlikely

Is Another Drug Suspected to Be Involved? _____

(If yes, gather the same information.)

TABLE 8.5 SERIOUS ADVERSE EXPERIENCE REPORTING

CONDITIONS	INVESTIGATOR	SPONSOR
Serious, life threatening, or fatal and associated with the use of drug and unexpected in nature, severity, or frequency	Phone call to sponsor Written safety report Follow-up reports Notify IRB	Initiate 7-day phone or fax report to the FDA Follow with 15-day written report Notify all sites
Serious and associated with the use of drug and unexpected in nature, severity, or frequency	Phone call to sponsor Written safety report Follow-up reports Notify IRB	Initiate 15-day written report to the FDA Notify sites

The sponsor representative (typically the Clinical Research Associate [CRA]) will then notify the medical monitor and, possibly, the project management team. Often the medical monitor, generally a physician, will become very involved in the management of the SAE.

3. **Immediately.** The investigator and his/her staff, in consultation with the sponsor representatives (the CRA, medical monitor, or project manager), will make some decisions regarding the subject and his/her participation in the trial. Often, there is an immediate need to make a medical decision in the clinical management of the subject. It is the responsibility of the investigator or subinvestigator to treat the subject as is clinically appropriate. The protocol may provide guidance as to how to handle an SAE. In further consultation with the sponsor, additional decisions include the following:
   - How should the subject's SAE be handled at this point?
   - Should the investigational agent be discontinued?
   - Should the subject be discontinued from the study? A subject must be discontinued from participation, especially administration of the investigational agent, if it is considered a medical risk to the subject by either the investigator or the sponsor.
4. **Within 7 days or 15 days of occurrence.** Reports to be completed and filed. Note: A MEDWATCH Form (FDA Form 3500A, Appendix B) may be used or the sponsor may supply specific forms for reporting SAE information. The MedWatch form can be downloaded from the following Web address: www.fda.gov/medwatch.

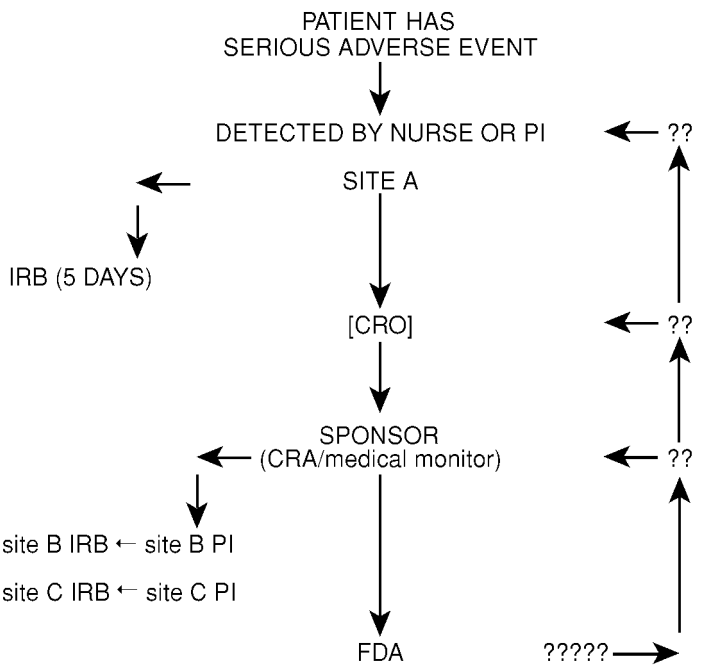
- If an SAE is SERIOUS (but not life threatening), UNEXPECTED, AND ASSOCIATED with the use of the investigational agent, the FDA must be notified. The sponsor must file a written IND Safety Report within 15 CALENDAR DAYS of notification of the SAE. The written report must contain information on all previous Safety Reports of similar events and an analysis of the significance of the events. All investigators must be notified within 15 calendar days. They must notify their IRBs of the IND Safety Report. Investigators and IRBs must consider whether the Informed Consent form must be modified to include the occurrence of the SAE.
- If an SAE is SERIOUS *AND* LIFE THREATENING OR FATAL, UNEXPECTED, AND ASSOCIATED with the use of the investigational agent, the FDA must be notified BY TELEPHONE OR FAX within 7 CALENDAR DAYS of the notification to the sponsor. The sponsor must follow up with a written IND Safety Report to the FDA within 15 CALENDAR DAYS. The written report must contain information on all similar events and an analysis of the significance of the events. All investigators must be notified within 15 calendar days. They must notify their IRBs of the IND Safety Report. Investigators and IRBs must consider whether the Informed Consent Form must be modified to include the occurrence of the SAE. Table 8.3 summarizes investigator and sponsor responsibilities in reporting serious adverse experiences.

5. **Within 5 working days.** The investigator must notify the IRB of an SAE occurring at the institution. Notification according to regulation should be "IMMEDIATE AND PROMPT."
6. **Ongoing.** Follow the subject until SAE subsides. Submit updated reports to sponsor and FDA as needed. Clinically significant signs, symptoms, or abnormalities must be followed until they return to normal or pretreatment status or are judged to be no longer clinically significant. The progress of the subject should be monitored, documented, and communicated to the sponsor and the FDA.

Figure 8.1 shows a schematic representation of reporting requirements of an SAE for an investigational agent under an IND application. SAEs in NIH studies can be reported under the AdEERS system electronically at http://webapps.ctep.nci.nih.gov. SAEs occurring in studies where data will be reported internationally (ICH) are generally reported on a CIOMS (Council for International Organizations of Medical Sciences) form.

FIGURE 8.1 REPORTING REQUIREMENTS FOR AN SAE: INVESTIGATIONAL AGENT

SAEs occurring under an IND application must be reported to the FDA. The FDA may respond with questions at a variety of levels.

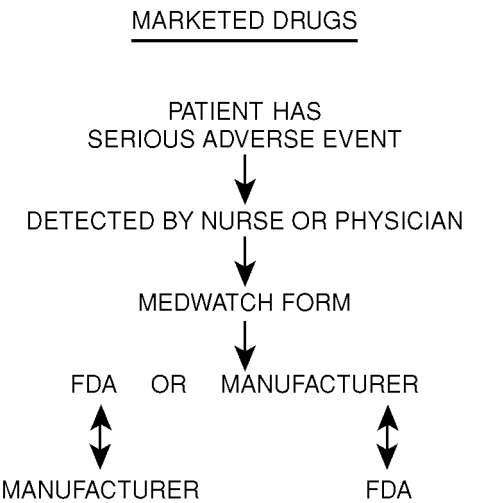


Once a drug has received FDA approval for marketing, SAEs must still be reported to the FDA. Postmarketing regulations are stipulated in 21 CFR 310.305 and 314.80.

During the first three years of marketing, the sponsor must submit quarterly reports of serious labeled AEs and nonserious unlabeled events as Periodic Reports. Serious, unlabeled events require a report to the FDA within 15 days of occurrence. Any increase in frequency of serious, labeled events must also be submitted to the FDA within 15 days.

The nurse or physician detecting the AE with a newly marketed drug is not likely to be involved in a clinical trial. These reports are spontaneously submitted by the medical professional to either the manufacturer or directly to the FDA. A MEDWATCH form (FDA Form 3500A, Appendix B) may be used to report AEs with marketed drugs or devices. Figure 8.2 is a schematic representation of reporting requirements for marketed drugs.

FIGURE 8.2 REPORTING REQUIREMENTS FOR AN SAE: MARKETED DRUG



HANDLING A SUBJECT DEATH IN A CLINICAL TRIAL

Deaths do occur in clinical trials. Sometimes, death is an expected endpoint. However, sudden, unexpected death during a clinical trial presents a very serious situation. When a sudden, unexpected subject death occurs, the following steps *must* be taken:

- CONTACT THE SPONSOR IMMEDIATELY.
- Gather general information on events surrounding patient's death.
- Attending physician requests an autopsy.
- Request lab information (pertinent clinical labs).
- Obtain blood samples (and CSF [cerebral spinal fluid], other tissue samples) for drug level.
- Review, in detail, subject's medical record and CRF.
- Verify compliance/check study drug.
- Check concurrent medications.
- Review past medical history.
- Retrieve the unused investigational agent.
- Notify the IRB.
- File report with the FDA (via sponsor).

The following steps should be *considered:*

- Discontinue dosing on all subjects (at all sites).
- Suspend enrollment in the clinical trial.
- Interview nurses, staff present at time of death.
- Question family on events surrounding death.
- Inform all subjects in the trial of a subject's death.

The following questions need to be addressed and decisions made in consultation with the sponsor:

- Is the event drug related?
- Should the study be stopped?
- Should dosing be restarted? How?
- Is this a dose-limiting toxicity?

It is likely that the sponsor will conduct a site visit immediately if a sudden, unexpected death occurs *and* it is thought to be related to the investigational agent.

After the initial event, it is necessary to

- continue to review incoming data;
- obtain final autopsy, test results;
- conduct intensive review of data;
- review all subject data for trends;
- check literature; and
- continue dialogue with the sponsor and the FDA.

If the death is determined to be related to the investigational agent, it may pose serious consequences for the future of the investigational agent. It may require modifications of the protocol, in dosing or in concurrent medications. Or, depending on the risk/benefit ratio, the investigational agent may be deemed too risky for further development.

If the death is determined to be NOT related to the investigational agent, then

- the study can be restarted, although there may need to be some modifications to account for the interruption;
- enrollment can continue; and
- everyone can breath a little easier!

REGULATORY REFERENCES

Serious Adverse Event Reporting

21 CFR 312.32, 312.64, and 310.305.

FDA Guideline for Reporting ABRs (21 CFR 600.80) (3/90).

Compliance Program Guidance Manual: Enforcement of the Adverse Drug Experience Reporting Regulations (5/91).
NIH Guidelines, January 2001 (www.nih.gov).

Postmarketing Reporting

21 CFR 314.80.

Guideline for Postmarketing Reporting of Adverse Drug Experiences (3/92).

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A Systematic Approach for Handling Adverse Events. Horst Nowak, *Drug Information Journal,* Vol. 27, pp. 1001–1007, 1993.

Adverse Drug Events: Identification and Attribution. A. Smith Rogers, *Drug Intelligence and Clinical Pharmacology,* Vol. 21, pp. 915–920, 1987.

Adverse Event Data Collection and Reporting: A Discussion of Two Grey Areas. J. Nickes, *Drug Information Journal,* Vol. 29 (4), pp. 1247–1251, 1995.

ASHP Guidelines on Adverse Drug Reaction Monitoring and Reporting. *Am. J. Hosp. Pharm.,* Vol. 46, pp. 336–337, 1989.

Clinical Trial Adverse Events: The Case for Descriptive Techniques. William Huster, *Drug Information Journal,* Vol. 25 (3), 1991.

From Bedside to Package Insert: Presentation of AEs in Product Labeling. T. Newman, *Drug Information Journal,* Vol. 29 (4), pp. 1263–1267, 1995.

Guidelines for the Management of Adverse Events Occurring During Clinical Trials. C. Benichou and G. Danan, *Drug Information Journal,* Vol. 25 (4), pp. 565–571, 1991.

Informing Subjects of Adverse Effects. Slobodan M. Jankovic, *Applied Clinical Trials,* Vol. 6 (3), p. 58, 1997.

Introducing MEDWATCH: A New Approach to Reporting Medication and Device Adverse Effects and Product Problems. David A. Kessler for the Working Group. *JAMA,* Vol. 269 (21), 1993. Reprinted in *Journal of Clinical Research and Drug Development,* Vol. 7 (3), 1993. (Reprint requests to Commissioner of Food and Drugs, FDA, 5600 Fishers Lane, Rockville, MD 20857.)

Reasonable Possibility: Causality and Postmarketing Surveillance. Joyce Johnson, *Drug Information Journal,* Vol. 26 (4), pp. 553–558, 1992.

Recognizing and Reporting Adverse Events. Alan Sugar, *Research Nurse*, Vol. 4 (3), pp. 1–7, 1998.

The FDA Desk Guide for Adverse Event and Product Problem Reporting

Available from:
Food and Drug Administration
MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
800-FDA-1088
http://www.fda.gov/medwatch (download form)

9

INVESTIGATIONAL AGENT MANAGEMENT

The term *investigational agent* refers to the study medication, or study drug, or experimental device to be used in a protocol. The use of investigational agents in clinical trials is strictly outlined by Food and Drug Administration (FDA) regulations. It is imperative that the agent can be accounted for at every step of the clinical trial process—from the sponsor's shipment to the site to its destruction by the sponsor or use by the subject. This chapter will focus primarily on investigational drug substances, although the same general principles apply to devices. The Principal Investigator (PI) is ultimately responsible for all investigational agents but may delegate authority to other individuals.

INVESTIGATIONAL DRUG AGENTS IN A CLINICAL TRIAL

Most study drugs and biologics are in the form of a solid or a liquid, but you may also see investigational agents in the form of a gas, such as an inhaled anesthetic used during surgery. Additionally, an approved drug may be studied for a different usage (unapproved indication) or assembled in a way different from the approved form. Whatever the investigational agent may be, the Clinical Research Coordinator (CRC) must keep in mind these responsibilities:

1. The drug is to be used only as specified in the protocol and is to be handled/administered only under the supervision of the physician approved to do the study (Principal Investigator [PI]) (21 CFR 312.61).
2. The FDA requires the investigator to establish a record of receipt, use, and disposition of all investigational agents (21 CFR 312.62).
3. The drug must be kept in a secure place (pharmacy or physician's office, secured clinic area) (21 CFR 312.69).

Before you receive an investigational agent(s), be sure you have a good understanding of the protocol and know what to expect in the way of study drugs and study design. Frequently, there will be mention of an active drug (the investigational agent) as well as a placebo ("sugar pill" or some similar inactive, innocuous substance). The study drug and the placebo are usually made to look identical. In some trials, the investigational agent is being compared to an approved form of treatment (active control arm). In this case, the study drugs will be designed to look alike, e.g., similar appearing capsules. If this is not possible, such as when one drug is an intravenous fluid and the other a tablet, placebos for each drug will be provided. Note that all of these are considered investigational agents and must be appropriately accounted for.

A study may be double blinded, meaning that neither the investigator nor the subjects knows whether they are receiving the study drug or placebo, or it may be a single-blinded study, meaning that only the subjects do not know which they are receiving.

The statistical analysis section of the protocol explains how the number of study subjects was determined as well as drug randomization. A computer-generated randomization pattern "assigns" the drug to the subject by subject number. Randomization by blocks is done to assure equal enrollment into each treatment group. If a study drug is randomized in groups of four, for example, this means that each group of four consecutive subject numbers was randomized separately from other subject numbers. Each group of four has the same number of active and placebo drug assigned. Separate blocks of four are randomized in different orders:

SUBJECT #	DRUG ASSIGNMENT	
1	A	
2	A	
3	P	
4	P	drug A =
5	A	active
6	P	
7	A	drug P =
8	P	placebo
9	P	
10	A	
11	A	
12	P	
etc.		

Other than for statistical significance, it is important to understand the randomization method used in the study to be sure the study number is assigned properly. If the CRC assigned the number "1" to the first subject, then "2" to the second subject, but "5" to the third subject, the randomization sequence has been broken, statistically speaking, this could make the study "biased" and ruin the study. ALWAYS ADMINISTER THE STUDY DRUG AND ASSIGN SUBJECT NUMBERS EXACTLY AS INSTRUCTED.

CODE BREAKERS

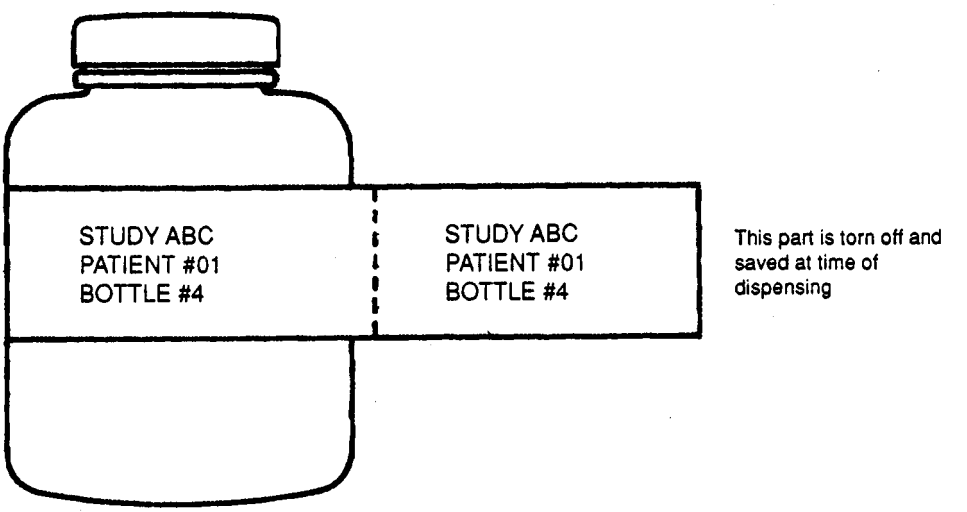
A code breaker gives the identity of the drugs assigned to each subject enrolled in a blinded study as determined by the randomization sequence. Ask the study sponsor whether there will be a code breaker for the study drug given to each study site. A code may be "broken" in the case of a serious, life-threatening event if it affects the treatment of the event. Usually, someone other than the investigator or the CRC should keep this to prevent "peeking" and bias in the study. Often it is kept by the investigational pharmacist in a place that is accessible 24 hours a day. Be sure you clearly understand the circumstances under which the code may be broken. Even if done when necessary and appropriately, statistical significance is lost each time the code is broken. Any time the code is broken, it will raise a red flag during an inspection.

STUDY DRUG LABELS

The labels used on study medication containers packaged for individual subjects are often "tear-off" labels. This means that one part of the label stays on the medication container, be it a bottle, vial, or blister card, and the other part is torn off at the time of dispensing and saved for drug records. An example of a tear-off label is in Figure 9.1.

Labels are important in study drug accountability records and should be kept in an orderly fashion in a safe place. Sometimes the identity of the drug is written and sealed inside the tear-off label and would be revealed only if the label were peeled back a certain way. In this case, the labels serve as both code breakers and drug accountability aids and must be locked up once the bottle is dispensed to prevent anyone from discovering the identity of the drug, thus unblinding the study. Never dispense the study medication to the subject with the tear-off portion attached; the subject may open the

FIGURE 9.1 EXAMPLE OF A TEAR-OFF LABEL



label and unblind himself/herself to the study medication and become ineligible for continued participation. Ask your sponsor representative how you should handle the tear-off labels, if the study containers have them.

The following sections will guide you in handling the investigational drug agent from the time it is received at the study site to the time it is either administered or destroyed.

RECEIVING AND STORING THE INVESTIGATIONAL AGENT

The pharmacy is usually the best-qualified department in an institution to receive and store study drug, but in some cases, alternate storage areas may be used:

- Area for drug storage and dispensing in the clinic.
- Private office medication storage area.
- Hospital satellite pharmacy.
- The investigator's office (locked).

The following are UNACCEPTABLE areas for storage:

- Desk drawer.
- Subject's hospital room.
- Open shelf in clinic or exam room.

Certain guidelines should be followed when finding a storage area for investigational drugs:

- The area must meet the requirements for storage of the drug (temperature, light).
- The area must be LOCKED and secured from unauthorized people.
- The space must be adequate.

Carefully review the protocol to determine the storage requirements and the QUANTITY of drug to be shipped. If each subject is dispensed 1 bottle every 2 weeks for a 3-year study with an anticipated enrollment of 100 subjects, you might have to move out of your office just to provide storage space! Work with the sponsor monitor to establish a shipment schedule that would provide enough drug to begin the study. It is then the responsibility of the CRC to assure that there will always be enough study drug on hand for subjects. Remember to allow lead time of about **4 to 6 weeks** for packaging and shipping subsequent orders.

When the box of investigational agent arrives, immediately examine the outer box to make sure there was no damage during shipping, open it carefully, and locate the shipping document in the container, which describes the contents of the shipment. Read the document completely and compare it to the actual contents found in the shipment box. If there is any discrepancy or question, call the sponsor IMMEDIATELY. If there are no problems with the shipment, sign the appropriate portion of the shipping document, if required, and return it to the sponsor. RETAIN A COPY IN THE STUDY FILE (OR SIMILAR PHARMACY FILES) AS A RECORD OF THE SHIPMENT FOR FUTURE REFERENCE.

The contents may be packaged in several ways:

Bulk Containers The liquid or solid form may arrive in large bulk containers from which the pharmacy may dispense study drug to multiple subjects. The drug agent name may be indicated if the study is not blinded, or the container may have a code name (like "Drug A") if the pharmacist/investigator is blinded. ALL SUCH IDENTIFIED

DRUGS MUST CONTAIN AN EMERGENCY CODE-BREAKING MECHANISM.

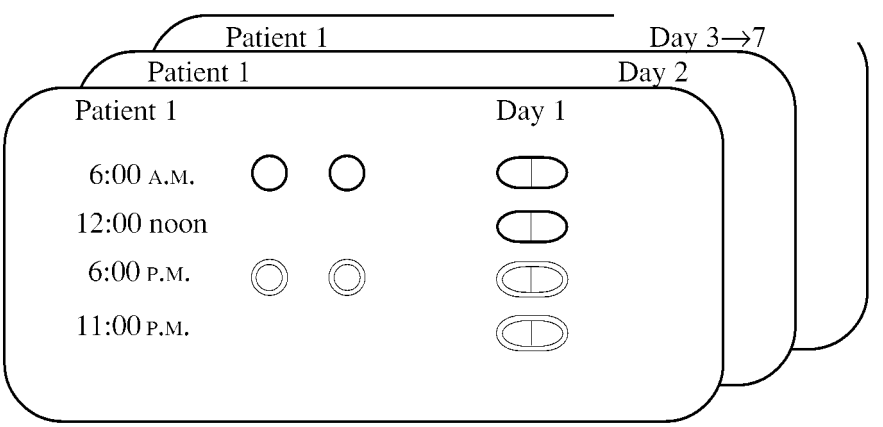
Individual Subject Containers

The study drug is divided into separate containers for each subject and is identified by subject numbers or by code name. The contents of each container are uniform—for example, there are not both active and placebo in each container. Multiple containers may be provided as a "subject kit."

Blister Cards

Study drug is packaged under clear plastic and attached to a card so that each dose (tablet or capsule) is separated under a "dome" and is clearly visible. The cards are usually set up according to dosing schedules for ease of subject compliance.

Here is an example of varying doses four times a day in a seven-day study.



DISPENSING THE INVESTIGATIONAL DRUG AGENT

There are many ways in which the study drug may be dispensed:

In-House Studies

- Prepared by pharmacist in the central pharmacy or satellite pharmacy.
- Delivered to the ward or dispensed to the CRC.

Outpatient Studies

- Dispensed directly by the pharmacist to the subject.
- Dispensed by the pharmacist to the CRC who dispenses the drug to the subject.
- Stored, prepared, and dispensed in the clinic area by the PI, CRC, or other qualified individual.

The investigational pharmacist will be one of the first people you will have to notify about the potential study subject. Be sure to let him/her know *before you begin screening subjects* that the study will begin as soon as a subject qualifies. If the study is blinded, the pharmacist will consult the procedure guidelines for assigning subject study numbers and study medication and will prepare the study medication for the CRC to pick up (or to dispense to the subject for outpatient studies). Double-check the study inclusion/exclusion criteria and be sure all necessary data points have been collected before administering or dispensing the study drug.

The subject has signed the Informed Consent Form and meets all study entry criteria, and your site has been given the green light to proceed with study enrollment. Time to begin!

Before administering or dispensing the investigational agent:

1. Be sure there is a written medication order by the investigator in the subject's chart.
2. Verify the dose to be given.
3. Identify the subject—if an inpatient, check the wrist band.
4. Administer the medication as ordered.
5. Record the dose (date, time, medication, dose, route) in the medication record, the subject chart, and the Case Report Form (CRF).

If the subject is to take the medication home for self-administration, be sure to do steps 1–3 first, then give the subject instructions on self-administration (see "Instructions to Study Subjects"). Record the identifiers of the study medication (date, time, dose, route, frequency, amount dispensed, bottle #) on both the CRF and the subject's chart. It is important to record the information in the subject record so that another healthcare provider unrelated to the study will be aware of the subject's study participation should the subject require treatment.

INSTRUCTIONS TO STUDY SUBJECTS

If the subject will be self-administering the study drug, it is extremely important that the drug be taken correctly. Give both oral and written instructions that are

1. as brief as possible,
2. clearly understandable to any nonmedical person, and
3. handy (either attached to the medicine container or on a small card that can fit in a wallet or pocket).

Items to include in the written instructions are as follows:

1. Exact dose in familiar dosage units, e.g., 2 pills instead of 2 mg.
2. Number of doses. It is best to relate the doses to specific times of the day rather than leaving that open to the subject. For example, indicate 8:00 A.M. and 8:00 P.M. instead of b.i.d. If possible, work with the subject's schedule to make dosing convenient without violating the protocol.
3. Highlight any restrictions, such as "take with food" or "take without food."
4. Provide instructions on storing the medication (refrigerate, avoid heat, etc.).
5. Instruct the subject to return all unused medication (including empty containers) and/or to bring the medication to EVERY appointment (for compliance checks).
6. Include the name and telephone number of someone who can answer questions.
7. Provide a brief synopsis of the study drug to give to healthcare personnel not familiar with the study in case of an emergency.
8. Provide diaries for subjects to record information.

Some suggestions:

- Write the instructions on the back of the subject's next appointment card.

front

Instructions

1. Take 1 tablet with food at breakfast, lunch, and dinner.
2. Keep refrigerated.
3. Return bottle at your next visit.

Contact: C. Menow 555.5555

back

- On a 3 × 5 card that can be laminated to preserve it through the study.

INSTRUCTIONS

1. Take 1 tablet with food at breakfast, lunch, and dinner.
2. Keep refrigerated.
3. Return bottle at your next visit.

Any questions? Contact C. Menow at 555-5555, beeper #315.

- Attached to the study drug container.

- Test the subject's understanding of the oral and written instructions by asking the subject to read them back to you and explain each step.
- A follow-up telephone call can be very helpful to assess subject understanding and compliance. If the subject does not have a telephone, ask for the nearest phone where you could leave a message or arrange a call-in time.

STUDY DRUG ACCOUNTABILITY

When you are working with an investigational drug, the FDA requires that you know where EVERY UNIT of drug is and how it was used from the time it arrived at your site until it was administered to the subject or returned to the pharmacy or sponsor for destruction. The key to accurate drug accountability is constant record-keeping, which becomes your "paper trail"—shipping documents, pharmacy records of drug preparation, and dispensing (drug accountability logs), subject medication records, subject's drug diary (if applicable), and pharmacy final inventory for destruction log.

Examples A and B are two flowcharts illustrating the route of an investigational drug. In both specific examples, the study drug passes through many pairs of hands from the time it is dispensed to the time it is returned. Because records are kept at each step of the way, it should be easy to track down any unit of study drug at any time. Note that appropriate entries also must be made in the CRF. Table 9.1 shows an example of an accountability form used for this important paper trail. Note that sometimes it is preferred to have one accountability page per patient (long-term studies with frequent visits) instead of one log for the whole study. The study sponsor will probably supply all the necessary forms for the study, but sometimes a pharmacy may be able to use its own forms if they are appropriate. ALWAYS record medication dispensing, returning, wasting, and so on AS YOU GO. You will not be able to remember details accurately if you wait until a later time to do the paperwork.

TABLE 9.1 DRUG ACCOUNTABILTY FORM

Form approved:
OMB No. 0925-0240
Expires: 1/31/2001

National Institutes of Health
National Cancer Institute

Division of Cancer Treatment and Diagnosis
Cancer Therapy Evaluation Program

PAGE NO.
CONTROL RECORD ☐
SATELLITE RECORD ☐

Investigational Agent Accountability Record

Name of Institution:	NCI Protocol No.:
Agent Name:	Dose Form and Strength:
Protocol Title:	Dispensing Area:
Investigator Name:	NCI Investigator No.:

Line No.	Date	Patient's Initials	Patient's ID No.	Dose	Quantity Dispensed or Received	Balance Forward / Balance	Manufacturer and Lot No.	Recorder's Initials
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								
11.								
12.								
13.								
14.								
15.								
16.								
17.								
18.								
19.								
20.								
21.								
22.								
23.								
24.								

NIH-2564

Example A Study patient #01 enters the study.

The pharmacist dispenses Bottle #1 for pt. #01 to the CRC.
Pharmacist records entry in drug accountability record.

↓

The CRC dispenses Bottle #1 to pt. #01.
CRC makes an entry in the clinic chart and CRF re: dispensed medication.

↓

Pt. #01 takes the bottle home, takes the exact amount as prescribed, returns in one week for study visit with Bottle #1 containing 2 tablets.

↓

The CRC verifies that 2 tablets remain and that pt. #01 has taken all medication as prescribed and enters this information on the clinic chart and CRF.

↓

CRC returns Bottle #1 to the pharmacy for the study sponsor to inventory at the next site visit.

↓

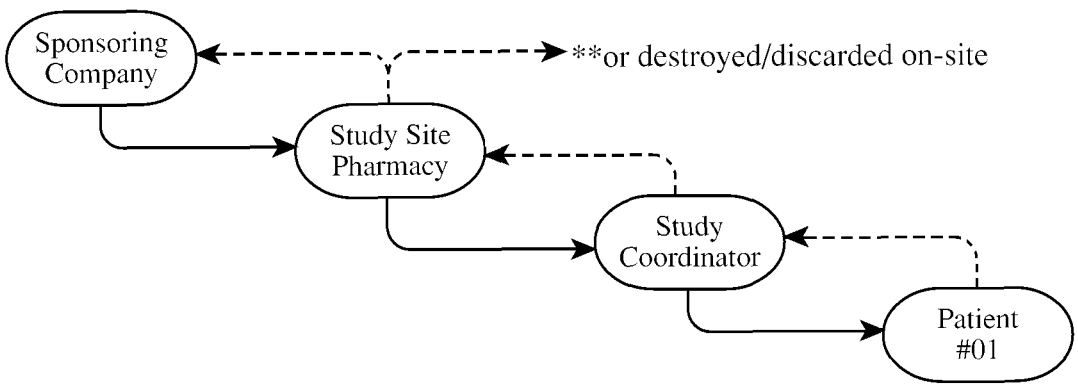
The pharmacist dispenses Bottle #2 for pt. #01 to the CRC.
Pharmacist records entry in drug accountability record.

↓

The CRC dispenses Bottle #2 to pt. #01.
CRC makes an entry in the clinic chart and CRF re: dispensed medication.

↓

When all bottles in the pharmacy have been inspected and accountability records are correct, Bottle #1 for pt. #01 will be destroyed or returned to the sponsor.



Example B Inpatient study involving study drug that is a liquid injection; the "unit" of drug in this case is a vial of liquid.

Study patient #01 enters the study.

Pharmacist draws up the dose of study drug in a syringe according to patient's weight (the used vial remains in the pharmacy) and logs out the amount in the drug accountability record.

↓

The CRC picks up the syringe to take to the patient.

↓

The dose is administered to pt. #01 and recorded in the medical chart and CRF.

↓

The CRC returns the empty syringe to the pharmacy to show that it was all used as dispensed.

↓

The pharmacist notes that none is remaining in the syringe and discards the empty syringe.

↓

The used vial for pt. #01 will remain on-site until the study sponsor inspects the accountability records.

DESTRUCTION OF THE INVESTIGATIONAL AGENT—FINAL DISPOSITION

Once the paper trail for each study subject is complete, and there are no outstanding or unaccounted for units of study drug, the remaining drug in each study container as well as the containers themselves are usually destroyed. The drug may be sent back to the manufacturer or sponsor for final counts and destruction or it may be destroyed on-site *with the study sponsor's approval* (include the written policy in the study file). Find out what final disposition policies the company wishes you to follow and prepare accordingly

before the study begins. If it is a large study with many vials or bottles and all containers must remain on-site until study completion, there must be space allocated for such bulk. The drug may be returned/destroyed before the study is completed if the sponsor checks the completed subjects' drug accountability logs at each site visit and approves disposition. Whatever the policy, do not discard any part of the investigational agent or the container without first consulting the sponsor.

On-site destruction must follow guidelines written by the Occupational Safety and Health Administration (OSHA), and most hospital pharmacies are aware of allowed methods for drug destruction. Most common methods are destruction by incineration, crushing, and autoclaving. Some liquids may be poured down the sink, capsules may be flushed IF THE EXPERIMENTAL AGENT POSES NO DANGER TO THE ENVIRONMENT SHOULD IT BECOME PART OF THE FOOD CHAIN. Containers may be recycled if clean or burned. The study drug cannot simply be thrown into the trash for fear someone might ingest it or use it in some other way that could cause harm to him/her. The sponsor monitor may require witnessing the destruction of the investigational agent.

After study completion, the drug accountability logs must be kept in the study files along with other study information for the appropriate time period. If the pharmacy requires that records be kept in its files, maintain a copy in the study files with a memo stating that the original may be located in the pharmacy files.

COMMON QUESTIONS

Following are some common questions and answers about investigational agent management:

1. What if some of the study drug is spilled or lost, or the vial is broken?
   Your first step is to call the sponsor, especially if the study is blinded and you need to replace the drug. It may be possible to use some of the subject's existing supply to get through the crisis. Record the incident in the drug accountability record and the subject's chart.

2. As the "investigational drug manager" in a cancer clinic, I noticed during a periodic inventory of study drugs that some drug was not recorded in the accountability log. What should I do?

There are many ways to locate the missing information (assuming it is the information that is missing and not the drug):

- Review subject charts. Sometimes study drug is not specifically identified to a subject; therefore, it may be necessary to review all charts of all subjects enrolled in the study. Determine which subjects received the drug and if it was logged out.
- Review CRFs until you can identify what had not been logged.
- Review what should have been dispensed; maybe too much or too little was dispensed.
- Determine who might have dispensed the drug and ask them if they recall who received the drug.
- You can narrow down when the drug was dispensed by the date in the log (either by what was dispensed chronologically, if the drug containers are numbered, or by the last time you did an inventory). Consult the appointment books to see which study subjects were in clinic and should have received treatment.

When you discover the missing entry, enter it in the log on the next line with a brief explanation (or write a longer explanation in a memo to file with the logs). Remember, if the study is audited five years later, someone is going to need the information to explain the entry.

3. My subjects often forget or "lose" their drug to be returned. How important is it to return the empty containers or partially used containers?
   It is very important. The FDA requires that you account for all study medication. Also, as the CRC, you will want to see returned medication to measure compliance. Reinforce the importance of this to the study subjects. Written instructions help. A phone call before the visit might also help those who chronically forget. In cases where the returned container is not retrievable, write a memo to the file so that there is a record (and so that everyone else doing accountability does not waste a lot of time looking for something that does not exist).

4. The study patient is lost to follow-up; how far should the CRC go to retrieve the study drug?

A valiant effort is needed here. In one study, the investigator went to the subject's funeral to retrieve study drug (1). Multiple phone calls are necessary. Some flexibility helps ("I'll meet you at the corner outside the clinic so you don't have to park"). You may even need to go to the subject's home (only if invited)—you may want to send the investigator if it's an unsafe part of town. In any case, DOCUMENT all attempts to retrieve the study drug even if unsuccessful.

5. Dr. Wan came to our clinic and requested some of the investigational drug for his laboratory studies. Can I log out the drug to him?
   NO! The investigational agent is to be used ONLY FOR THE CLINICAL TRIAL. The same investigational drug supply (unless open-label and intended to be used in more than one trial) cannot be used in two different clinical trials with the same drug. NEVER switch drugs between studies. NEVER give clinical trial supplies for laboratory research use.

6. Why should I record information in both the drug accountability logs and the patient CRF?
   The dispensing of study drug should be recorded in at least three places:
   - Drug accountability log: Keeps track exclusively of all study drug. Must be maintained with the study files and is used to inventory study drug and determine usage and disposition.
   - CRF: Records the actual amount of study drug given to the subject. This is the information that will be entered into the database for analysis.
   - Source document (medical record/clinic chart): This is the record that will become a part of the subject's medical history and may impact his/her medical care.

REGULATORY REFERENCES

Code of Federal Regulations, Title 21, Parts 312.59, 312.61, 312.62, and 312.69.

Recordkeeping in Clinical Investigations (10/95).

"Investigational Drug Accountability Record" (forms and instructions from the National Cancer Institute). Request copies from

Drug Management and Authorization Section
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment
National Cancer Institute
P.O. Box 30012
Bethesda, MD 20814

NOTE

(1) When Murphy's Law Runs Rampant. B. Padbury, *Drug Information Journal*, Vol. 26 (3), pp. 421–423, 1992.

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10

INSPECTION OF CLINICAL RESEARCH SITES

All clinical trials are subject to review by a higher authority—the Food and Drug Administration (FDA), the sponsor, the OHRP (Office for Human Research Protection), National Institutes of Health (NIH), or other cooperative group/grants management auditing team. Some institutions and Institutional Review Boards (IRBs) also have internal auditing committees to look after their own trials. Can you avoid an audit? Not really, but you can be prepared for one!

All of the activities that occur during a clinical trial should be undertaken with the attitude that an inspection is likely to happen, usually after the study is completed. It is, therefore, in the best interest of everyone to conduct the trial according to regulations, for the sponsor to regularly monitor the trial, and to retain all records of the trial for the required time period.

WHO, WHY, AND WHAT

Who Can Audit a Clinical Trial?

FDA

The Bioresearch Monitoring Program was established in 1977, and its activities include inspections of clinical investigators, sponsors, biopharmaceutical laboratories, IRBs, and toxicology laboratories:

> The purpose of the compliance programs is to (1) assess adherence to FDA regulation, (2) determine the validity of specific studies in support of products pending approval by the FDA, and (3) determine that the rights

and safety of subjects used in clinical studies have been properly protected. (*FDA Compliance Program Manual*, Part 1, page 2)

OHRP

The OHRP, under the Department of Health and Human Services, has the authority to audit institutions conducting human research and to suspend research at the institution where there are violations of human subject's rights.

The Sponsor of the Clinical Trial

In addition to periodic monitoring of clinical trials, the sponsor also may have a Compliance Department that is independent of the Clinical Research group doing the trial. Specific purposes of auditing by a sponsor include the following:

> (1) help insure that clinical monitors are doing their job accurately, (2) help insure that investigators and staff are doing their job appropriately, (3) help insure that future regulatory inspections will be smooth and uneventful, (4) help insure that the data will be suitable for a regulatory submission (5) help insure that the clinical development process is conducted as efficiently as possible. [Spilker, *DN&P* 3(5), June 1990]

Cooperative Groups

Many cooperative groups set up audit committees to audit members. In the Cancer and Leukemia Group B (CALGB) handbook, the purposes are to ensure that

> (1) protocol rules and guidelines have been adhered to; (2) that the information that was submitted on [CALGB] data forms is accurate and complete; (3) that all requirements regarding the protection of human subjects have been adhered to; (4) that [NCI] guidelines pertaining to investigational drugs have been followed by the institution. (*CALGB Data Manager's Handbook*, Section F: "Audit Guidelines," page F-1)

IRBs and Institutions

IRBs and institutions also have the right to inspect clinical trials and observe the research process (21 CFR 56.109), especially if they suspect something is amiss.

Who Can Be Inspected by the FDA?

- Clinical investigators and staff.
- Sponsors of clinical trials (pharmaceutical companies for clinical trial conduct and manufacturing).
- Clinical research organizations (CROs).
- Clinical monitors.
- IRBs.
- Preclinical facilities (toxicology labs).
- Clinical laboratories.
- Manufacturing facilities.

Why Are Studies Audited?

FDA

Routine surveillance inspections (study-oriented inspections): The FDA routinely inspects randomly selected sites to audit as part of the Bioresearch Monitoring Program. The FDA also audits pivotal trials supporting a New Drug Application (NDA) to verify data accuracy.

"For cause" inspections (investigator-oriented inspections): A "for cause" inspection may be initiated for any of the following reasons:

- The investigator has participated in a large number of studies.
- The investigator has done work outside of his/her specialty.
- The investigator has made safety or efficacy findings that are inconsistent with those at other study sites.
- The investigator enrolls more subjects for the disease than seems reasonable for the locale or setting of the practice.

- The investigator reports lab results that are outside the range of expected biological variation (or identical).
- The sponsor reports to the FDA problems identified with the site (e.g., lack of data submissions).
- A study subject makes a complaint to the FDA about alleged protocol violations or violation of subject's rights.

Bioequivalence study inspection: Conducted because one bioequivalence study may be the sole basis for the marketing approval of the drug.

Sponsor

Routine surveillance: The company wants to assure that the investigative staff and sponsor monitoring staff are doing their jobs appropriately, consistently, and according to company procedure.

In preparation for an FDA inspection: The company may conduct a "preaudit" visit to assist the investigator in preparing for an FDA inspection.

Cooperative Groups or Grant-Funded Research

To justify placing a grant, continue funding, or to verify data.

IRBs and Institutions

To assure that institution policies and IRB regulations are being followed.

What?

Usually the FDA inspector or person conducting the audit will want to

1. determine who was in control of the study; how the study was conducted by the investigator and his staff; how much was delegated; and whether the investigator oversaw all activities, such as review and signing of Case Report Forms (CRFs) and dispensing of investigational agent to study subjects only.
2. review the facilities for adequacy.
3. determine adherence to the protocol.
4. know how and where data were recorded and stored.

5. audit data: subject rights, subject safety, validity of data (source document checks).
6. audit study files for adherence to regulations and Good Clinical Practices (GCPs).
7. monitor sponsor interaction (how often and why was the study monitored).
8. determine investigational agent accountability.

Results

Inspections by the FDA result in one of the following types of letters:

NAI — *No action indicated:* No findings requiring action.

VAI — *Voluntary action indicated:* Some findings were noted, and the investigator should attempt to address the situation and respond in writing to the FDA district office.

OAI — *Official action indicated:* Serious discrepancies were found. The investigator must rectify the situation and respond in writing to the FDA district office. It is likely that the investigator will be inspected again to assure that the situation has improved. Failure to resolve discrepancies to the satisfaction of the FDA may result in the FDA taking further action against the investigator.

Audits by other groups may result in loss of sponsor funding for future trials or loss of grant/cooperative group participation. The FDA will be alerted to serious infractions.

What to Do If Called for an Inspection by the FDA

- Cooperate with the inspector in setting a date for the inspection.
- Try to determine the reason for the inspection and for which study.
- Find out who will be conducting the inspection. How many people coming and from where?
- Ask what records will be needed (subject files, labs, study files, etc.).
- Notify sponsor immediately.
- Notify the IRB immediately.
- Don't panic.

It is imperative to cooperate and schedule a date for an inspection. In signing the Statement of Investigator form (Form FDA 1572), the investigator agrees to make records available for inspection in accordance with 21 CFR 312.68. The FDA will not consider results of a study conducted by an investigator who refuses an FDA inspection, and this may lead to blacklisting the investigator for further studies.

PREPARING FOR AN INSPECTION

Once the inspection is scheduled, the Clinical Research Coordinator (CRC) and investigator need to prepare for the visit. Hopefully, the investigator was able to get specific details (e.g., which study or studies, what type of inspection) when the inspection was scheduled. This will help in preparing for the visit.

Things to Do Before the Inspection

- Reserve a space for the inspector to work (you may need a room equipped with special medical equipment, such as an X-ray box, if X rays were part of the study).
- Notify and make appointments with other personnel with whom the inspector may wish to speak (subinvestigators, investigative staff, pharmacist, other specialists, etc.).
- Gather necessary information (see Table 10.1). NOTE: If you are working with adjunct groups or satellite groups, obtain all relevant information and have it available at the main site for the audit.
- Review and organize the information listed in Table 10.1: Obtain any missing items. DO NOT MAKE CHANGES TO DATA ALREADY SUBMITTED FOR ANALYSIS. The goal is "damage control." What can you do before the audit? There are things that you should not do—don't dig a deeper hole trying to fix something. However, do not attempt to hide information or point out information to the inspector.
- Meet with the investigational staff—discuss the study, raise concerns. Make sure everyone is on the same track (get the facts straight).

TABLE 10.1 CHECKLIST OF THINGS TO GATHER FOR INSPECTION

NAME OF PROTOCOL _____ **NUMBER** _____

INVESTIGATOR _____ **CRC** _____

DATE INITIATED _____ **DATE COMPLETED** _____

NUMBER OF SUBJECTS ENROLLED _____ **PATIENT NUMBERS** _____

AUXILIARY STAFF _____

Any specific information requested by the inspector (cooperative group audits will often provide a specific list of patients for data audits):

STUDY FILES

☐ Statement of Investigator (Form FDA 1572)	Signed and current as of date of beginning of the study (all copies—include initial as well as amended forms).
☐ Curriculum Vitae	Current as of beginning of study, updated as needed (have CVs of sub-investigators available).
IRB Approvals and Correspondence	☐ Submission of protocol or investigational plan to IRB for approval prior to the start of the study. ☐ Initial approval letter. ☐ Approved version of Informed Consent Form. ☐ Annual renewals (some IRBs require more frequent renewals/updates). ☐ Submission and approval of amendments (change in consent form?). ☐ Investigational New Drug (IND) Safety Reports and serious adverse events (SAEs) (change in consent form?). ☐ Progress reports. ☐ Final study report. ☐ Assurance that IRB meets FDA requirements.
Correspondence Between Investigator and Sponsor	☐ All correspondence (budget information may be omitted). Organize chronologically. ☐ Other study-related correspondence, e.g., letters to testing centers, labs.
Informed Consent Forms	☐ Blank copy of all IRB–approved versions. (Date and organize chronologically. Be prepared to back up with documents any changes in Informed Consent Form during the course of the study.) ☐ Original signed copies of study participants' Informed Consent Forms OBTAINED PRIOR TO ENTRY INTO STUDY (if the original form is required to be kept in the subject's medical record chart, obtain copies for this file, but have immediate access to the original for the inspection).
Protocol	☐ Original signed version. ☐ All amended versions. ☐ All changes documented and reported to sponsor.
Investigator's Brochure	☐ All versions. ☐ Include any updated information received through the course of the study (e.g., reports of new adverse events or new study results).
☐ Study Procedure's Manual	Copy of the manual or other informational resources used during the study.
☐ Monitoring Log	A log of all monitoring visits by the sponsor.
☐ Subject Screening Log	Not always required. A log of subjects considered for studies is often required for cooperative groups to ascertain nonbias in subject selection.

Table 10.1 continued on next page

Table 10.1 continued from previous page

☐	Telephone Monitoring Log or Reports	Documentation of phone conversations with the sponsor or study subject.
☐	Material Subject Log	To identify subjects for notification of new information.

INVESTIGATIONAL AGENT RECORDS

☐	Person authorized to dispense/administer test article.	
☐	Investigational Agent Shipping Records	(Obtain originals from pharmacy, if necessary.)
☐	Investigational Agent Dispensing/ Accountability Records	☐ Obtain originals from pharmacy, if necessary. ☐ Showing receipt date and quantity. ☐ Date, quantity dispensed, and subject identification. ☐ Date, quantity returned to sponsor or destroyed.
☐	Randomization Code	(To ensure subjects enrolled according to protocol.)
☐	Location/Storage Facility	☐ Adequate for storage of investigational agent. ☐ Restricted access.
☐	No promotional material claiming efficacy has been disseminated by the investigator.	

SUBJECT RECORDS

	CRFs	☐ Blank copy of all versions. ☐ Completed and *signed* copies for each study participant.
	Subject Records	☐ Clinic charts. ☐ Hospital medical record. ☐ Appointment books. ☐ Hospital census records. ☐ Clinical lab results.
☐	Special Tests	File of tests required for the study but not part of the subject's permanent record (e.g., study drug levels.)
☐	Serious Adverse Event Reporting Forms	Blank copies supplied by sponsor (if not supplied, a MEDWATCH form may be kept on file).
☐	Serious Adverse Event Reports	Completed copies of all SAE information occurring at this site for this study. Include copies of relevant labs.
☐	IND Safety Reports	Reports of SAEs at *any* site submitted by the sponsor to the FDA. Must be submitted to IRB.

CLINICAL LABORATORY

☐	Clinical Laboratory Certification	Current for entire length of study. May be many certifications. Organize by lab and then chronologically.
☐	Clinical Laboratory Normal Value Ranges	Should be a separate set for EACH DIFFERENT lab used during the study.

BUDGET *It is not required to submit budget records for FDA inspection.*

On the Day of the Inspection

The CRC should plan to spend the entire time with the inspector. The investigator should also be available for the entire time of the inspection to respond to questions.

DO

- Ask to see credentials. The inspector should present a Form FDA 482 "Notice of Inspection."
- Have *all* subject records (CRFs and source documents) organized and available. Give the inspector ONLY those records specifically requested.
- Make scrupulous notes of comments/concerns/deficiencies pointed out by the inspector.
- Question entries in the inspector's notes regarding adverse findings.
- Clarify or attempt to resolve issues as they are made known. Investigate those items pointed out by the inspector and try to RESOLVE THEM immediately to avoid an entry on the Establishment Inspection Report (EIR).
- If the questions seems vague, ask for clarification before answering. Make sure the inspector understands your response.
- Be courteous, professional, and available.
- Make requested copies (also make a second copy for your records), locate documents, records, etc.
- Object to requests for unreasonable information (for example, financial records or home addresses of subjects). In this case, the investigator may ask for a written request from the FDA (but you will probably have to produce the information).
- Let the sponsor know of the outcome as soon as possible.

DO NOT

- DO NOT GIVE MORE INFORMATION THAN ASKED FOR. Limit comments to concise, accurate replies to specific questions.

- DO NOT OFFER TO CHANGE DATA UNLESS IT CAN BE VERIFIED WITH THE SPONSOR and supported by source documents.
- DO NOT DISCUSS OTHER STUDIES.
- DO NOT discuss financial arrangements between you and the sponsor or make those files available.
- DO NOT hide information or volunteer information.
- DO NOT sign affidavits.
- DO NOT allow pictures.
- DO NOT leave the inspector alone.
- DO NOT make any truth statements.
- DO NOT initial/sign any errors.

THE DATA AUDIT

An important aspect of the inspection is an intense audit of the subject records—the data audit. The inspector wants to verify that the subjects exist and were available for all visits, and that the data were recorded and reported accurately. Table 10.2 lists some specific questions commonly asked.

AT THE END OF THE INSPECTION

The FDA inspector issues a Form FDA 483. The investigator should read this report carefully and respond IMMEDIATELY to any inaccuracies; have the inspector make corrections to the report. If not satisfied, respond in writing to the FDA district office. The investigator must sign the Form 483. In about 6 months, an EIR will become available. The investigator must request a copy of the EIR. Anyone may request a copy of the report through the Freedom of Information (FOI) Act. Respond to inaccuracies and document the resolution of cited problems to the FDA district office and REQUEST that the response letter be made available through the FOI Act so that the public record is accurate. The FDA will then issue one of the three letters: NAI, VAI, or OAI.

TABLE 10.2 COMMON QUESTIONS FOR A DATA AUDIT

- Was proper informed consent obtained?
- Was the subject randomized correctly?
- Was the subject ELIGIBLE for the study (review and verification of all inclusion/exclusion criteria)?
- Is there evidence that the subject was available for the study as indicated (records of clinic visits, hospitalization records, etc.)?
- Did all of the subjects have a history of the condition being studied?
- Were all protocol-required tests performed at the designated times?
- Were all doses taken appropriately?
- Were all adverse events noted?
- Were any SAEs reported to the FDA and the IRB?
- Are the response variables recorded and accurate?
- Were any subjects discontinued from the study? Why? Were they reported to the sponsor?
- Do source documents exist?
- Are the data supported by source documentation?
- Are there any missing records?
- Were the records altered in any way?
- Are the data too consistent?
- How do the data compare to data collected at other sites?
- Was the study blind maintained?

REGULATORY REFERENCES

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IRB Compliance Program Guidance Manual.

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Detecting Fraud Using Auditing and Biometrical Methods. Jurgen Schmidt, Heiner Gertzen, K. Michael Aschenbrenner, and Steen Ryholt-Jensen, *Applied Clinical Trials,* Vol. 4 (5), p. 50, 1995.

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ABBREVIATIONS

Following is a brief list of common abbreviations used in the conduct of clinical trials.

ACP	Association of Clinical Pharmacology (now ACRP)
ACRP	Association of Clinical Research Professionals
ADE	Adverse Drug Experience
ADME	absorption, distribution, metabolism, excretion
ADR	Adverse Drug Reaction
AE	Adverse Event, Adverse Experience
ANDA	Abbreviated New Drug Application
BSA	body surface area
CANDA	Computer-Assisted New Drug Application
CBER	Center for Biologics Evaluation and Research
CCRA	Certified Clinical Research Associate
CCRC	Certified Clinical Research Coordinator
CDC	Centers for Disease Control
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvements Amendments
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form, Case Record Form
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
CTX	Clinical Trial Exemption
CV	curriculum vitae

DHHS	Department of Health and Human Services
DIA	Drug Information Association
DOD	Department of Defense
DRG	diagnosis-related groups
	Division of Research Grants (NIH)
DSMB	Data and Safety Monitoring Board
EC	European Commission
EIR	Establishment Inspection Report
FDA	Food and Drug Administration
FDLI	Food and Drug Law Institute
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HHS	(U.S. Department of) Health and Human Services
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
JCAH	Joint Commission for the Accreditation of Hospitals
MTD	maximum tolerated dose
NAF	notice of adverse findings
NAI	no action indicated
NCE	New Chemical Entity
NDA	New Drug Application
NIH	National Institutes of Health
NME	New Molecular Entity
OAI	official action indicated
OHRP	Office of Human Research Protection (formerly OPRR)
OIG	Office of the Inspector General
OPRR	Office of Protection from Research Risks
OSHA	Occupational Safety and Health Administration
OTC	over-the-counter

PD	pharmacodynamics
PERI	Pharmaceutical Education and Research Institute
PhRMA	Pharmaceutical Research and Manufacturers of America
PHS	Public Health Service
PI	Principal Investigator
	package insert
PK	pharmacokinetics
PLA	Product License Application
PMA	Premarket Approval (Application)
PPI	patient package insert
RDE	remote data entry
SMO	site management organization
SOP	Standard Operating Procedure
SUD	sudden unexpected death
TIND	Treatment Investigational New Drug
TMO	trial management organization
VAI	voluntary action indicated
WHO	World Health Organization
WHOART	World Health Organization Adverse Reaction Terminology

Resources for additional abbreviations:

Glossary: Acronyms, Abbreviations, and Initials. *Applied Clinical Trials,* Vol. 4 (12), pp. 22–28, December 1995.

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Appendix A
FDA REGULATIONS

CFR, Title 21, Part 50: Protection of Human Subjects

CFR, Title 21, Part 56: Institutional Review Boards

CFR, Title 21, Part 312: Investigational New Drug Applcation
(Subpart D – Responsibilities of Sponsors and Investigators)

CFR, Title 45, Part 46: Protection of Human Subjects
(Subparts B, C, D)

AUTHORITY: 21 U.S.C. 321, 346, 346a, 348, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b–263n.

SOURCE: 45 FR 36390, May 30, 1980, unless otherwise noted.

Subpart A—General Provisions

§ 50.1 Scope.

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 406, 409, 502, 503, 505, 510, 513–516, 518–520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354–360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 36390, May 30, 1980; 46 FR 8979, Jan. 27, 1981, as amended at 63 FR 26697, May 13, 1998; 64 FR 399, Jan. 5, 1999]

§ 50.3 Definitions.

As used in this part:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201—902, 52 Stat. 1040 *et seq.* as amended (21 U.S.C. 321—392)).

(b) *Application for research or marketing permit* includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§ 170.30 and 570.30.

(4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in § 180.1.

(5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) [Reserved]

(12) An application for a biologics license, described in part 601 of this chapter.

(13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing,

amending, or repealing a standard for these products, described in part 809.

(15) An *Application for an Investigational Device Exemption*, described in part 812.

(16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.

(17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.

(18) An application for premarket approval of a medical device, described in section 515.

(19) A product development protocol for a medical device, described in section 515.

(20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.

(21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in § 1010.4.

(22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in § 1010.5.

(c) *Clinical investigation* means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

(d) *Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e) *Sponsor* means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(f) *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

(g) *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

(h) *Institution* means any public or private entity or agency (including Federal, State, and other agencies). The word *facility* as used in section 520(g) of the act is deemed to be synonymous with the term *institution* for purposes of this part.

(i) *Institutional review board* (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase *institutional review committee* as used in section 520(g) of the act.

(j) *Test article* means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354–360F of the

Public Health Service Act (42 U.S.C. 262 and 263b–263n).

(k) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(l) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's particpation in the procedure(s) involved in the research.

(m) *Family member* means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

[45 FR 36390, May 30, 1980, as amended at 46 FR 8950, Jan. 27, 1981; 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 61 FR 51528, Oct. 2, 1996; 62 FR 39440, July 23, 1997; 64 FR 399, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999]

Subpart B—Informed Consent of Human Subjects

SOURCE: 46 FR 8951, Jan. 27, 1981, unless otherwise noted.

§ 50.20 General requirements for informed consent.

Except as provided in §§ 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

[46 FR 8951, Jan. 27, 1981, as amended at 64 FR 10942, Mar. 8, 1999]

§ 50.23 Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

(d)(1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of

an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements of section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved the Secretary of Defense must first request such a determination from the President, and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met.

(i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND.

(ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness.

(iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug.

(iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission.

(v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by § 56.115(a)(2) of this chapter.

(vi) DOD has explained:

(A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional;

(B) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and

(C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

(vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient.

(viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.

(ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section.

(x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter.

(xi) DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

(xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence.

(xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request.

(xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use.

(xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria.

(xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent.

(xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in the FEDERAL REGISTER describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

(xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law.

(2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain any necessary security clearances. This IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by § 56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review.

(3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve:

(i) The required information sheet;

(ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written);

(iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and

(iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved.

(4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

(5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations.

[46 FR 8951, Jan. 27, 1981, as amended at 55 FR 52817, Dec. 21, 1990; 64 FR 399, Jan. 5, 1999; 64 FR 54188, Oct. 5, 1999]

§ 50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is

a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with § 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the

subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with § 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under §§ 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

[61 FR 51528, Oct. 2, 1996]

§ 50.25 Elements of informed consent.

(a) *Basic elements of informed consent.* In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be

maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) *Additional elements of informed consent.* When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

§ 50.27 Documentation of informed consent.

(a) Except as provided in § 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

(b) Except as provided in § 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(2) A *short form* written consent document stating that the elements of informed consent required by § 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

[46 FR 8951, Jan. 27, 1981, as amended at 61 FR 57280, Nov. 5, 1996]

pertaining to the financial interests of clinical investigators who conducted studies on which the application relies and who are not full or part-time employees of the applicant, as follows:

(1) Complete records showing any financial interest or arrangement as described in §54.4(a)(3)(i) paid to such clinical investigators by the sponsor of the covered study.

(2) Complete records showing significant payments of other sorts, as described in §54.4(a)(3)(ii), made by the sponsor of the covered clinical study to the clinical investigator.

(3) Complete records showing any financial interests held by clinical investigators as set forth in §54.4(a)(3)(iii) and (a)(3)(iv).

(b) *Requirements for maintenance of clinical investigators' financial records.*

(1) For any application submitted for a covered product, an applicant shall retain records as described in paragraph (a) of this section for 2 years after the date of approval of the application.

(2) The person maintaining these records shall, upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to and copy and verify these records.

PART 56—INSTITUTIONAL REVIEW BOARDS

Subpart A—General Provisions

Subpart B—Organization and Personnel

Subpart C—IRB Functions and Operations

Subpart D—Records and Reports

Subpart E—Administrative Actions for Noncompliance

AUTHORITY: 21 U.S.C. 321, 346, 346a, 348, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b–263n.

SOURCE: 46 FR 8975, Jan. 27, 1981, unless otherwise noted.

Subpart A—General Provisions

§56.101 Scope.

(a) This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[46 FR 8975, Jan. 27, 1981, as amended at 64 FR 399, Jan. 5, 1999]

§56.102 Definitions.

As used in this part:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201–902, 52 Stat. 1040 *et seq.*, as amended (21 U.S.C. 321–392)).

(b) *Application for research or marketing permit* includes:

(1) A color additive petition, described in part 71.

(2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §170.35.

(3) A food additive petition, described in part 171.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in §180.1.

(5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information regarding an over-the-counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) An application for a biologics license, described in part 601 of this chapter.

(11) Data and information regarding a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, as described in part 601 of this chapter.

(12) An *Application for an Investigational Device Exemption*, described in parts 812 and 813.

(13) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in part 860.

(14) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in part 861.

(15) An application for premarket approval of a medical device for human use, described in section 515 of the act.

(16) A product development protocol for a medical device for human use, described in section 515 of the act.

(17) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act.

(18) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in §1010.4.

(19) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in §1010.5.

(20) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003.

(c) *Clinical investigation* means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies.

The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous for purposes of this part.

(d) *Emergency use* means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

(e) *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

(f) *Institution* means any public or private entity or agency (including Federal, State, and other agencies). The term *facility* as used in section 520(g) of the act is deemed to be synonymous with the term *institution* for purposes of this part.

(g) *Institutional Review Board (IRB)* means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase *institutional review committee* as used in section 520(g) of the act.

(h) *Investigator* means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) *Sponsor* means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(k) *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.

(l) *Test article* means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354–360F of the Public Health Service Act.

(m) *IRB approval* means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

[46 FR 8975, Jan. 27, 1981, as amended at 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 64 FR 399, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 65 FR 52302, Aug. 29, 2000]

§ 56.103 Circumstances in which IRB review is required.

(a) Except as provided in §§ 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

(b) Except as provided in §§ 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or

marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

[46 FR 8975, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981]

§56.104 Exemptions from IRB requirement.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]

§56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

Subpart B—Organization and Personnel

§56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable catgory of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the instituton's consideration of qualified persons of both

sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

[46 FR 8975, Jan 27, 1981, as amended at 56 FR 28028, June 18, 1991; 56 FR 29756, June 28, 1991]

Subpart C—IRB Functions and Operations

§ 56.108 IRB functions and operations.

In order to fulfill the requirements of these regulations, each IRB shall:

(a) Follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.

(c) Except when an expedited review procedure is used (see § 56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910–0130)

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]

§ 56.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 50.25. The IRB may require that information, in addition to that specifically mentioned in § 50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent in accordance with § 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of

harm to subjects and involves no procedures for which written consent is normally required outside the research context; or

(2) The IRB may, for some or all subjects, find that the requirements in §50.24 of this chapter for an exception from informed consent for emergency research are met.

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(e) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. For investigations involving an exception to informed consent under §50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under §50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.

(f) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(g) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under §50.24 of this chapter a copy of information that has been publicly disclosed under §50.24(a)(7)(ii) and (a)(7)(iii) of this chapter. The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.

[46 FR 8975, Jan. 27, 1981, as amended at 61 FR 51529, Oct. 2, 1996]

§56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Food and Drug Administration has established, and published in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the FEDERAL REGISTER.

(b) An IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited review procedure set forth in §56.108(c).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

§56.111 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall

determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by § 50.27.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

§ 56.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§ 56.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

§ 56.114 Cooperative research.

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

Subpart D—Records and Reports

§ 56.115 IRB records.

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents,

progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

(6) Written procedures for the IRB as required by §56.108 (a) and (b).

(7) Statements of significant new findings provided to subjects, as required by §50.25.

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

(c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910–0130)

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

Subpart E—Administrative Actions for Noncompliance

§56.120 Lesser administrative actions.

(a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.

(b) On the basis of the IRB's or the institution's response, FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the agency may:

(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;

(2) Direct that no new subjects be added to ongoing studies subject to this part;

(3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or

(4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.

(c) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent

institution determined to be responsible for formal designation of the IRB.

§ 56.121 Disqualification of an IRB or an institution.

(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under § 56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in part 16.

(b) The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:

(1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and

(2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

(c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in the FEDERAL REGISTER.

(d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in § 56.123.

§ 56.122 Public disclosure of information regarding revocation.

A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under part 20.

§ 56.123 Reinstatement of an IRB or an institution.

An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under § 56.121(c).

§ 56.124 Actions alternative or additional to disqualification.

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.

PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

Subpart A—General Provisions

Subpart B—Organization and Personnel

Subpart D—Responsibilities of Sponsors and Investigators

Subpart E—Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

Subpart F—Miscellaneous

Subpart G—Drugs for Investigational Use in Laboratory Research Animals or in Vitro Tests

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371; 42 U.S.C. 262.

SOURCE: 52 FR 8831, Mar. 19, 1987, unless otherwise noted.

Subpart A—General Provisions

§ 312.1 Scope.

(a) This part contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's). An investigational new drug for which an IND is in effect in accordance with this part is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.

(b) References in this part to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§ 312.2 Applicability.

(a) *Applicability.* Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 *et seq.*)).

(b) *Exemptions.* (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a

significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of §312.7.

(2)(i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (*a*) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (*b*) it is shipped in compliance with §312.160.

(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (*a*) blood grouping serum; (*b*) reagent red blood cells; and (*c*) anti-human globulin.

(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with §312.160.

(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

(6) A clinical investigation involving an exception from informed consent under §50.24 of this chapter is not exempt from the requirements of this part.

(c) *Bioavailability studies.* The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of §320.31.

(d) *Unlabeled indication.* This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.

(e) *Guidance.* FDA may, on its own initiative, issue guidance on the applicability of this part to particular investigational uses of drugs. On request, FDA will advise on the applicability of this part to a planned clinical investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51529, Oct. 2, 1996; 64 FR 401, Jan. 5, 1999]

§312.3 Definitions and interpretations.

(a) The definitions and interpretations of terms contained in section 201 of the Act apply to those terms when used in this part:

(b) The following definitions of terms also apply to this part:

Act means the Federal Food, Drug, and Cosmetic Act (secs. 201–902, 52 Stat. 1040 *et seq.*, as amended (21 U.S.C. 301–392)).

Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

Contract research organization means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

FDA means the Food and Drug Administration.

IND means an investigational new drug application. For purposes of this part, "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug."

Investigational new drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or 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. "Subinvestigator" includes any other individual member of that team.

Marketing application means an application for a new drug submitted under section 505(b) of the act or a biologics license application for a biological product submitted under the Public Health Service Act.

Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

Sponsor-Investigator means 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 under this part include both those applicable to an investigator and a sponsor.

Subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

[52 FR 8831, Mar. 19, 1987, as amended at 64 FR 401, Jan. 5, 1999; 64 FR 56449, Oct. 20, 1999]

§ 312.6 Labeling of an investigational new drug.

(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug—Limited by Federal (or United States) law to investigational use."

(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

§ 312.7 Promotion and charging for investigational drugs.

(a) *Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

(b) *Commercial distribution of an investigational new drug.* A sponsor or investigator shall not commercially distribute or test market an investigational new drug.

(c) *Prolonging an investigation.* A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

(d) *Charging for and commercialization of investigational drugs*—(1) *Clinical trials under an IND.* Charging for an investigational drug in a clinical trial under an IND is not permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered part of the normal cost of doing business.

(2) *Treatment protocol or treatment IND.* A sponsor or investigator may charge for an investigational drug for a

treatment use under a treatment protocol or treatment IND provided: (i) There is adequate enrollment in the ongoing clinical investigations under the authorized IND; (ii) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (iii) the drug is not being commercially promoted or advertised; and (iv) the sponsor of the drug is actively pursuing marketing approval with due diligence. FDA must be notified in writing in advance of commencing any such charges, in an information amendment submitted under §312.31. Authorization for charging goes into effect automatically 30 days after receipt by FDA of the information amendment, unless the sponsor is notified to the contrary.

(3) *Noncommercialization of investigational drug.* Under this section, the sponsor may not commercialize an investigational drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug.

(4) *Withdrawal of authorization.* Authorization to charge for an investigational drug under this section may be withdrawn by FDA if the agency finds that the conditions underlying the authorization are no longer satisfied.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 19476, May 22, 1987]

§312.10 Waivers.

(a) A sponsor may request FDA to waive applicable requirement under this part. A waiver request may be submitted either in an IND or in an information amendment to an IND. In an emergency, a request may be made by telephone or other rapid communication means. A waiver request is required to contain at least one of the following:

(1) An explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved;

(2) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds that the sponsor's noncompliance would not pose a significant and unreasonable risk to human subjects of the investigation and that one of the following is met:

(1) The sponsor's compliance with the requirement is unnecessary for the agency to evaluate the application, or compliance cannot be achieved;

(2) The sponsor's proposed alternative satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

Subpart B—Investigational New Drug Application (IND)

§312.20 Requirement for an IND.

(a) A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to §312.2(a).

(b) A sponsor shall not begin a clinical investigation subject to §312.2(a) until the investigation is subject to an IND which is in effect in accordance with §312.40.

(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under §50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization from FDA. FDA shall provide a written determination 30 days after FDA receives the IND or earlier.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51529, Oct. 2, 1996; 62 FR 32479, June 16, 1997]

§312.21 Phases of an investigation.

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially,

they may overlap. These three phases of an investigation are a follows:

(a) *Phase 1.* (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

(b) *Phase 2.* Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

(c) *Phase 3.* Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

§ 312.22 General principles of the IND submission.

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

(d) The IND format set forth in § 312.23 should be followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed

for a commercially sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format, but ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

§312.23 IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

(1) *Cover sheet (Form FDA–1571).* A cover sheet for the application containing the following:

(i) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.

(ii) Identification of the phase or phases of the clinical investigation to be conducted.

(iii) A commitment not to begin clinical investigations until an IND covering the investigations is in effect.

(iv) A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research activity in accordance with the requirements of part 56.

(v) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

(vi) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.

(vii) The name(s) and title(s) of the person(s) responsible under §312.32 for review and evaluation of information relevant to the safety of the drug.

(viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

(ix) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(2) *A table of contents.*

(3) *Introductory statement and general investigational plan.* (i) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

(ii) A brief summary of previous human experience with the drug, with reference to other IND's if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s).

(iii) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (*a*) The rationale for the drug or the research study; (*b*)

the indication(s) to be studied; (*c*) the general approach to be followed in evaluating the drug; (*d*) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate); (*e*) the estimated number of patients to be given the drug in those studies; and (*f*) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

(4) [Reserved]

(5) *Investigator's brochure.* If required under § 312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

(6) *Protocols.* (i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with § 312.30(a).) In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation—an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose—and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(*a*) A statement of the objectives and purpose of the study.

(*b*) The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(*c*) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

(*d*) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

(*e*) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

(*f*) A description of the observations and measurements to be made to fulfill the objectives of the study.

(*g*) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

(7) *Chemistry, manufacturing, and control information.* (i) As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(iii) As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

(iv) Reflecting the distinctions described in this paragraph (a)(7), and based on the phase(s) to be studied, the submission is required to contain the following:

(*a*) *Drug substance.* A description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies. Reference to the current edition of the United States Pharmacopeia—National Formulary may satisfy relevant requirements in this paragraph.

(*b*) *Drug product.* A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug product manufacturer; a brief general description of the manufacturing and packaging procedure as appropriate for the product; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product; and information sufficient to assure the product's stability during the planned clinical studies. Reference to the current edition of the United States Pharmacopeia—National Formulary may satisfy certain requirements in this paragraph.

(*c*) A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.

(*d*) *Labeling.* A copy of all labels and labeling to be provided to each investigator.

(e) *Environmental analysis requirements.* A claim for categorical exclusion under § 25.30 or 25.31 or an environmental assessment under § 25.40.

(8) *Pharmacology and toxicology information.* Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i) *Pharmacology and drug disposition.* A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) *Toxicology.* (*a*) An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(*b*) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

(iii) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58, a statement that the study was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(9) *Previous human experience with the investigational drug.* A summary of previous human experience known to the applicant, if any, with the investigational drug. The information is required to include the following:

(i) If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. If the durg has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(ii) If the drug is a combination of drugs previously investigated or marketed, the information required under paragraph (a)(9)(i) of this section should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

(iii) If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

(10) *Additional information.* In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i) *Drug dependence and abuse potential.* If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii) *Radioactive drugs.* If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii) *Pediatric studies.* Plans for assessing pediatric safety and effectiveness.

(iv) *Other information.* A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

(11) *Relevant information.* If requested by FDA, any other relevant information needed for review of the application.

(b) *Information previously submitted.* The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously must identify the file by name, reference number, volume, and page number where the information can be found. A reference to information submitted to the agency by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(c) *Material in a foreign language.* The sponsor shall submit an accurate and complete English translation of each part of the IND that is not in English. The sponsor shall also submit a copy of each original literature publication for which an English translation is submitted.

(d) *Number of copies.* The sponsor shall submit an original and two copies of all submissions to the IND file, including the original submission and all amendments and reports.

(e) *Numbering of IND submissions.* Each submission relating to an IND is required to be numbered serially using a single, three-digit serial number. The initial IND is required to be numbered 000; each subsequent submission (e.g., amendment, report, or correspondence) is required to be numbered chronologically in sequence.

(f) *Identification of exception from informed consent.* If the investigation involves an exception from informed consent under §50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in §50.24 of this chapter.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 61 FR 51529, Oct. 2, 1996; 62 FR 40599, July 29, 1997; 63 FR 66669, Dec. 2, 1998; 65 FR 56479, Sept. 19, 2000]

§312.30 Protocol amendments.

Once an IND is in effect, a sponsor shall amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application. This section sets forth the provisions under which new protocols may be submitted and changes in previously submitted protocols may be made. Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in §50.24 of this chapter, the sponsor shall submit a separate IND for such investigation.

(a) *New protocol.* Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to FDA a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met: (1) The sponsor has submitted the protocol to FDA for its review; and (2) the protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of part

56. The sponsor may comply with these two conditions in either order.

(b) *Changes in a protocol.* (1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:

(i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

(ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

(iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(2)(i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:

(*a*) The sponsor has submitted the change to FDA for its review; and

(*b*) The change has been approved by the IRB with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.

(ii) Notwithstanding paragraph (b)(2)(i) of this section, a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with § 56.104(c).

(c) *New investigator.* A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under § 312.34. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

(d) *Content and format.* A protocol amendment is required to be prominently identified as such (i.e., "Protocol Amendment: New Protocol", "Protocol Amendment: Change in Protocol", or "Protocol Amendment: New Investigator"), and to contain the following:

(1)(i) In the case of a new protocol, a copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols.

(ii) In the case of a change in protocol, a brief description of the change and reference (date and number) to the submission that contained the protocol.

(iii) In the case of a new investigator, the investigator's name, the qualifications to conduct the investigation, reference to the previously submitted protocol, and all additional information about the investigator's study as is required under § 312.23(a)(6)(iii)(*b*).

(2) Reference, if necessary, to specific technical information in the IND or in a concurrently submitted information amendment to the IND that the sponsor relies on to support any clinically significant change in the new or amended protocol. If the reference is made to supporting information already in the IND, the sponsor shall identify by name, reference number, volume, and page number the location of the information.

(3) If the sponsor desires FDA to comment on the submission, a request for such comment and the specific questions FDA's response should address.

(e) *When submitted.* A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals.

When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 61 FR 51530, Oct. 2, 1996]

§312.31 Information amendments.

(a) *Requirement for information amendment.* A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:

(1) New toxicology, chemistry, or other technical information; or

(2) A report regarding the discontinuance of a clinical investigation.

(b) *Content and format of an information amendment.* An information amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: Chemistry, Manufacturing, and Control", "Information Amendment: Pharmacology-Toxicology", "Information Amendment: Clinical"), and to contain the following:

(1) A statement of the nature and purpose of the amendment.

(2) An organized submission of the data in a format appropriate for scientific review.

(3) If the sponsor desires FDA to comment on an information amendment, a request for such comment.

(c) *When submitted.* Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more than every 30 days.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988]

§312.32 IND safety reports.

(a) *Definitions.* The following definitions of terms apply to this section:–

Associated with the use of the drug. There is a reasonable possibility that the experience may have been caused by the drug.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience. Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by

virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) *Review of safety information.* The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor.

(c) *IND safety reports.* (1) *Written reports*—(i) The sponsor shall notify FDA and all participating investigators in a written IND safety report of:

(A) Any adverse experience associated with the use of the drug that is both serious and unexpected; or

(B) Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form; reports from animal or epidemiological studies shall be submitted in a narrative format) and shall bear prominent identification of its contents, i.e., "IND Safety Report." Each written notification to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. If FDA determines that additional data are needed, the agency may require further data to be submitted.

(ii) In each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previouos, similar reports.

(2) *Telephone and facsimile transmission safety reports.* The sponsor shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

(3) *Reporting format or frequency.* FDA may request a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the new drug review division in the Center for Drug Evaluation and Research or the director of the products review division in the Center for Biologics Evaluation and Research which is responsible for review of the IND.

(4) A sponsor of a clinical study of a marketed drug is not required to make a safety report for any adverse experience associated with use of the drug that is not from the clinical study itself.

(d) *Followup.* (1) The sponsor shall promptly investigate all safety information received by it.

(2) Followup information to a safety report shall be submitted as soon as the relevant information is available.

(3) If the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor

shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made.

(4) Results of a sponsor's investigation of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

(e) *Disclaimer.* A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse experience.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11579, Mar. 29, 1990; 62 FR 52250, Oct. 7, 1997]

§312.33 Annual reports.

A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation that includes:

(a) *Individual study information.* A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

(3) If the study has been completed, or if interim results are known, a brief description of any available study results.

(b) *Summary information.* Information obtained during the previous year's clinical and nonclinical investigations, including:

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

(2) A summary of all IND safety reports submitted during the past year.

(3) A list of subjects who died during participation in the investigation, with the cause of death for each subject.

(4) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trails, and information about bioavailability.

(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

(7) A summary of any significant manufacturing or microbiological changes made during the past year.

(c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under §312.23(a)(3)(iv).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect

to the IND for which the sponsor requests or expects a reply, comment, or meeting.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 63 FR 6862, Feb. 11, 1998]

§ 312.34 Treatment use of an investigational new drug.

(a) *General.* A drug that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available. During the clinical investigation of the drug, it may be appropriate to use the drug in the treatment of patients not in the clinical trials, in accordance with a treatment protocol or treatment IND. The purpose of this section is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness. In the case of a serious disease, a drug ordinarily may be made available for treatment use under this section during Phase 3 investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for treatment use during Phase 2. In the case of an immediately life-threatening disease, a drug may be made available for treatment use under this section earlier than Phase 3, but ordinarily not earlier than Phase 2. For purposes of this section, the "treatment use" of a drug includes the use of a drug for diagnostic purposes. If a protocol for an investigational drug meets the criteria of this section, the protocol is to be submitted as a treatment protocol under the provisions of this section.

(b) *Criteria.* (1) FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:

(i) The drug is intended to treat a serious or immediately life-threatening disease;

(ii) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;

(iii) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and

(iv) The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

(2) *Serious disease.* For a drug intended to treat a serious disease, the Commissioner may deny a request for treatment use under a treatment protocol or treatment IND if there is insufficient evidence of safety and effectiveness to support such use.

(3) *Immediately life-threatening disease.* (i) For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:

(A) May be effective for its intended use in its intended patient population; or

(B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

(ii) For the purpose of this section, an "immediately life-threatening" disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

(c) *Safeguards.* Treatment use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the IND process, including the regulations governing informed consent (21 CFR part 50) and institutional review boards (21 CFR part 56) and the applicable provisions of part 312, including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports.

(d) *Clinical hold.* FDA may place on clinical hold a proposed or ongoing

treatment protocol or treatment IND in accordance with § 312.42.

[52 FR 19476, May 22, 1987, as amended at 57 FR 13248, Apr. 15, 1992]

§ 312.35 Submissions for treatment use.

(a) *Treatment protocol submitted by IND sponsor.* Any sponsor of a clinical investigation of a drug who intends to sponsor a treatment use for the drug shall submit to FDA a treatment protocol under § 312.34 if the sponsor believes the criteria of § 312.34 are satisfied. If a protocol is not submitted under § 312.34, but FDA believes that the protocol should have been submitted under this section, FDA may deem the protocol to be submitted under § 312.34. A treatment use under a treatment protocol may begin 30 days after FDA receives the protocol or on earlier notification by FDA that the treatment use described in the protocol may begin.

(1) A treatment protocol is required to contain the following:

(i) The intended use of the drug.

(ii) An explanation of the rationale for use of the drug, including, as appropriate, either a list of what available regimens ordinarily should be tried before using the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments.

(iii) A brief description of the criteria for patient selection.

(iv) The method of administration of the drug and the dosages.

(v) A description of clinical procedures, laboratory tests, or other measures to monitor the effects of the drug and to minimize risk.

(2) A treatment protocol is to be supported by the following:

(i) Informational brochure for supplying to each treating physician.

(ii) The technical information that is relevant to safety and effectiveness of the drug for the intended treatment purpose. Information contained in the sponsor's IND may be incorporated by reference.

(iii) A commitment by the sponsor to assure compliance of all participating investigators with the informed consent requirements of 21 CFR part 50.

(3) A licensed practioner who receives an investigational drug for treatment use under a treatment protocol is an "investigator" under the protocol and is responsible for meeting all applicable investigator responsibilities under this part and 21 CFR parts 50 and 56.

(b) *Treatment IND submitted by licensed practitioner.* (1) If a licensed medical practitioner wants to obtain an investigational drug subject to a controlled clinical trial for a treatment use, the practitioner should first attempt to obtain the drug from the sponsor of the controlled trial under a treatment protocol. If the sponsor of the controlled clinical investigation of the drug will not establish a treatment protocol for the drug under paragraph (a) of this section, the licensed medical practitioner may seek to obtain the drug from the sponsor and submit a treatment IND to FDA requesting authorization to use the investigational drug for treatment use. A treatment use under a treatment IND may begin 30 days after FDA receives the IND or on earlier notification by FDA that the treatment use under the IND may begin. A treatment IND is required to contain the following:

(i) A cover sheet (Form FDA 1571) meeting § 312.23(g)(1).

(ii) Information (when not provided by the sponsor) on the drug's chemistry, manufacturing, and controls, and prior clinical and nonclinical experience with the drug submitted in accordance with § 312.23. A sponsor of a clinical investigation subject to an IND who supplies an investigational drug to a licensed medical practitioner for purposes of a separate treatment clinical investigation shall be deemed to authorize the incorporation-by-reference of the technical information contained in the sponsor's IND into the medical practitioner's treatment IND.

(iii) A statement of the steps taken by the practitioner to obtain the drug under a treatment protocol from the drug sponsor.

(iv) A treatment protocol containing the same information listed in paragraph (a)(1) of this section.

(v) A statement of the practitioner's qualifications to use the investigational drug for the intended treatment use.

(vi) The practitioner's statement of familiarity with information on the drug's safety and effectiveness derived from previous clinical and nonclinical experience with the drug.

(vii) Agreement to report to FDA safety information in accordance with § 312.32.

(2) A licensed practitioner who submits a treatment IND under this section is the sponsor-investigator for such IND and is responsible for meeting all applicable sponsor and investigator responsibilities under this part and 21 CFR parts 50 and 56.

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[52 FR 19477, May 22, 1987, as amended at 57 FR 13249, Apr. 15, 1992]

§ 312.36 Emergency use of an investigational new drug.

Need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in accordance with § 312.23 or § 312.34. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of an IND. A request for such authorization may be transmitted to FDA by telephone or other rapid communication means. For investigational biological drugs, the request should be directed to the Division of Biological Investigational New Drugs (HFB–230), Center for Biologics Evaluation and Research, 8800 Rockville Pike, Bethesda, MD 20892, 301–443–4864. For all other investigational drugs, the request for authorization should be directed to the Document Management and Reporting Branch (HFD–53), Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4320. After normal working hours, eastern standard time, the request should be directed to the FDA Division of Emergency and Epidemiological Operations, 202–857–8400. Except in extraordinary circumstances, such authorization will be conditioned on the sponsor making an appropriate IND submission as soon as practicable after receiving the authorization.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11579, Mar. 29, 1990]

§ 312.38 Withdrawal of an IND.

(a) At any time a sponsor may withdraw an effective IND without prejudice.

(b) If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with § 312.59.

(c) If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

Subpart C—Administrative Actions

§ 312.40 General requirements for use of an investigational new drug in a clinical investigation.

(a) An investigational new drug may be used in a clinical investigation if the following conditions are met:

(1) The sponsor of the investigation submits an IND for the drug to FDA; the IND is in effect under paragraph (b) of this section; and the sponsor complies with all applicable requirements in this part and parts 50 and 56 with respect to the conduct of the clinical investigations; and

(2) Each participating investigator conducts his or her investigation in compliance with the requirements of this part and parts 50 and 56.

(b) An IND goes into effect:

(1) Thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under §312.42; or

(2) On earlier notification by FDA that the clinical investigations in the IND may begin. FDA will notify the sponsor in writing of the date it receives the IND.

(c) A sponsor may ship an investigational new drug to investigators named in the IND:

(1) Thirty days after FDA receives the IND; or

(2) On earlier FDA authorization to ship the drug.

(d) An investigator may not administer an investigational new drug to human subjects until the IND goes into effect under paragraph (b) of this section.

§312.41 Comment and advice on an IND.

(a) FDA may at any time during the course of the investigation communicate with the sponsor orally or in writing about deficiencies in the IND or about FDA's need for more data or information.

(b) On the sponsor's request, FDA will provide advice on specific matters relating to an IND. Examples of such advice may include advice on the adequacy of technical data to support an investigational plan, on the design of a clinical trial, and on whether proposed investigations are likely to produce the data and information that is needed to meet requirements for a marketing application.

(c) Unless the communication is accompanied by a clinical hold order under §312.42, FDA communications with a sponsor under this section are solely advisory and do not require any modification in the planned or ongoing clinical investigations or response to the agency.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

§312.42 Clinical holds and requests for modification.

(a) *General.* A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

(b) *Grounds for imposition of clinical hold*—(1) *Clinical hold of a Phase 1 study under an IND.* FDA may place a proposed or ongoing Phase 1 investigation on clinical hold if it finds that:

(i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;

(ii) The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;

(iii) The investigator brochure is misleading, erroneous, or materially incomplete; or

(iv) The IND does not contain sufficient information required under §312.23 to assess the risks to subjects of the proposed studies.

(v) The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (i.e., affecting reproductive organs) or developmental toxicity (i.e., affecting potential offspring). The phrase "women with reproductive potential" does not include pregnant women. For purposes of this paragraph, "life-threatening illnesses or diseases" are defined as "diseases or conditions where the likelihood of death is high unless the course

of the disease is interrupted.'' The clinical hold would not apply under this paragraph to clinical studies conducted:

(A) Under special circumstances, such as studies pertinent only to one gender (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function);

(B) Only in men or women, as long as a study that does not exclude members of the other gender with reproductive potential is being conducted concurrently, has been conducted, or will take place within a reasonable time agreed upon by the agency; or

(C) Only in subjects who do not suffer from the disease or condition for which the drug is being studied.

(2) *Clinical hold of a Phase 2 or 3 study under an IND.* FDA may place a proposed or ongoing Phase 2 or 3 investigation on clinical hold if it finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(v) of this section apply; or

(ii) The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

(3) Clinical hold of a treatment IND or treatment protocol.

(i) *Proposed use.* FDA may place a proposed treatment IND or treatment protocol on clinical hold if it is determined that:

(A) The pertinent criteria in § 312.34(b) for permitting the treatment use to begin are not satisfied; or

(B) The treatment protocol or treatment IND does not contain the information required under § 312.35 (a) or (b) to make the specified determination under § 312.34(b).

(ii) *Ongoing use.* FDA may place an ongoing treatment protocol or treatment IND on clinical hold if it is determined that:

(A) There becomes available a comparable or satisfactory alternative drug or other therapy to treat that stage of the disease in the intended patient population for which the investigational drug is being used;

(B) The investigational drug is not under investigation in a controlled clinical trial under an IND in effect for the trial and not all controlled clinical trials necessary to support a marketing application have been completed, or a clinical study under the IND has been placed on clinical hold;

(C) The sponsor of the controlled clinical trial is not pursuing marketing approval with due diligence;

(D) If the treatment IND or treatment protocol is intended for a serious disease, there is insufficient evidence of safety and effectiveness to support such use; or

(E) If the treatment protocol or treatment IND was based on an immediately life-threatening disease, the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:

(*1*) May be effective for its intended use in its intended population; or

(*2*) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

(iii) FDA may place a proposed or ongoing treatment IND or treatment protocol on clinical hold if it finds that any of the conditions in paragraph (b)(4)(i) through (b)(4)(viii) of this section apply.

(4) *Clinical hold of any study that is not designed to be adequate and well-controlled.* FDA may place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if it finds that:

(i) Any of the conditions in paragraph (b)(1) or (b)(2) of this section apply; or

(ii) There is reasonable evidence the investigation that is not designed to be adequate and well-controlled is impeding enrollment in, or otherwise interfering with the conduct or completion of, a study that is designed to be an adequate and well-controlled investigation of the same or another investigational drug; or

(iii) Insufficient quantities of the investigational drug exist to adequately conduct both the investigation that is not designed to be adequate and well-controlled and the investigations that are designed to be adequate and well-controlled; or

(iv) The drug has been studied in one or more adequate and well-controlled investigations that strongly suggest lack of effectiveness; or

(v) Another drug under investigation or approved for the same indication and available to the same patient population has demonstrated a better potential benefit/risk balance; or

(vi) The drug has received marketing approval for the same indication in the same patient population; or

(vii) The sponsor of the study that is designed to be an adequate and well-controlled investigation is not actively pursuing marketing approval of the investigational drug with due diligence; or

(viii) The Commissioner determines that it would not be in the public interest for the study to be conducted or continued. FDA ordinarily intends that clinical holds under paragraphs (b)(4)(ii), (b)(4)(iii) and (b)(4)(v) of this section would only apply to additional enrollment in nonconcurrently controlled trials rather than eliminating continued access to individuals already receiving the investigational drug.

(5) *Clinical hold of any investigation involving an exception from informed consent under §50.24 of this chapter.* FDA may place a proposed or ongoing investigation involving an exception from informed consent under §50.24 of this chapter on clinical hold if it is determined that:

(i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or

(ii) The pertinent criteria in §50.24 of this chapter for such an investigation to begin or continue are not submitted or not satisfied.

(6) Clinical hold of any investigation involving an exception from informed consent under §50.23(d) of this chapter. FDA may place a proposed or ongoing investigation involving an exception from informed consent under §50.23(d) of this chapter on clinical hold if it is determined that:

(i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or

(ii) A determination by the President to waive the prior consent requirement for the administration of an investigational new drug has not been made.

(c) *Discussion of deficiency.* Whenever FDA concludes that a deficiency exists in a clinical investigation that may be grounds for the imposition of clinical hold FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order.

(d) *Imposition of clinical hold.* The clinical hold order may be made by telephone or other means of rapid communication or in writing. The clinical hold order will identify the studies under the IND to which the hold applies, and will briefly explain the basis for the action. The clinical hold order will be made by or on behalf of the Division Director with responsibility for review of the IND. As soon as possible, and no more than 30 days after imposition of the clinical hold, the Division Director will provide the sponsor a written explanation of the basis for the hold.

(e) *Resumption of clinical investigations.* An investigation may only resume after FDA (usually the Division Director, or the Director's designee, with responsibility for review of the IND) has notified the sponsor that the investigation may proceed. Resumption of the affected investigation(s) will be authorized when the sponsor corrects the deficiency(ies) previously cited or otherwise satisfies the agency that the investigation(s) can proceed. FDA may notify a sponsor of its determination regarding the clinical hold by telephone or other means of rapid communication. If a sponsor of an IND that has been placed on clinical hold requests in writing that the clinical hold be removed and submits a complete response to the issue(s) identified in the clinical hold order, FDA shall respond in writing to the sponsor within 30-calendar days of receipt of the request and the complete response. FDA's response will either remove or maintain the clinical hold, and will state the reasons for such determination. Notwithstanding the 30-calendar day response time, a sponsor may not proceed with a clinical trial on which a clinical hold has been imposed until the sponsor has been notified by FDA that the hold has been lifted.

(f) *Appeal.* If the sponsor disagrees with the reasons cited for the clinical hold, the sponsor may request reconsideration of the decision in accordance with §312.48.

(g) *Conversion of IND on clinical hold to inactive status.* If all investigations covered by an IND remain on clinical hold for 1 year or more, the IND may be placed on inactive status by FDA under § 312.45.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 19477, May 22, 1987; 57 FR 13249, Apr. 15, 1992; 61 FR 51530, Oct. 2, 1996; 63 FR 68678, Dec. 14, 1998; 64 FR 54189, Oct. 5, 1999; 65 FR 34971, June 1, 2000]

§ 312.44 Termination.

(a) *General.* This section describes the procedures under which FDA may terminate an IND. If an IND is terminated, the sponsor shall end all clinical investigations conducted under the IND and recall or otherwise provide for the disposition of all unused supplies of the drug. A termination action may be based on deficiencies in the IND or in the conduct of an investigation under an IND. Except as provided in paragraph (d) of this section, a termination shall be preceded by a proposal to terminate by FDA and an opportunity for the sponsor to respond. FDA will, in general, only initiate an action under this section after first attempting to resolve differences informally or, when appropriate, through the clinical hold procedures described in § 312.42.

(b) *Grounds for termination*—(1) *Phase 1.* FDA may propose to terminate an IND during Phase 1 if it finds that:

(i) Human subjects would be exposed to an unreasonable and significant risk of illness or unjury.

(ii) The IND does not contain sufficient information required under § 312.23 to assess the safety to subjects of the clinical investigations.

(iii) The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for subject safety.

(iv) The clinical investigations are being conducted in a manner substantially different than that described in the protocols submitted in the IND.

(v) The drug is being promoted or distributed for commercial purposes not justified by the requirements of the investigation or permitted by § 312.7.

(vi) The IND, or any amendment or report to the IND, contains an untrue statement of a material fact or omits material information required by this part.

(vii) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of serious and unexpected adverse experiences in accordance with § 312.32 or fails to make any other report required under this part.

(viii) The sponsor fails to submit an accurate annual report of the investigations in accordance with § 312.33.

(ix) The sponsor fails to comply with any other applicable requirement of this part, part 50, or part 56.

(x) The IND has remained on inactive status for 5 years or more.

(xi) The sponsor fails to delay a proposed investigation under the IND or to suspend an ongoing investigation that has been placed on clinical hold under § 312.42(b)(4).

(2) *Phase 2 or 3.* FDA may propose to terminate an IND during Phase 2 or Phase 3 if FDA finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(xi) of this section apply; or

(ii) The investigational plan or protocol(s) is not reasonable as a bona fide scientific plan to determine whether or not the drug is safe and effective for use; or

(iii) There is convincing evidence that the drug is not effective for the purpose for which it is being investigated.

(3) FDA may propose to terminate a treatment IND if it finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (x) of this section apply; or

(ii) Any of the conditions in § 312.42(b)(3) apply.

(c) *Opportunity for sponsor response.* (1) If FDA proposes to terminate an IND, FDA will notify the sponsor in writing, and invite correction or explanation within a period of 30 days.

(2) On such notification, the sponsor may provide a written explanation or correction or may request a conference with FDA to provide the requested explanation or correction. If the sponsor does not respond to the notification

within the allocated time, the IND shall be terminated.

(3) If the sponsor responds but FDA does not accept the explanation or correction submitted, FDA shall inform the sponsor in writing of the reason for the nonacceptance and provide the sponsor with an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be terminated. The sponsor's request for a regulatory hearing must be made within 10 days of the sponsor's receipt of FDA's notification of nonacceptance.

(d) *Immediate termination of IND.* Notwithstanding paragraphs (a) through (c) of this section, if at any time FDA concludes that continuation of the investigation presents an immediate and substantial danger to the health of individuals, the agency shall immediately, by written notice to the sponsor from the Director of the Center for Drug Evaluation and Research or the Director of the Center for Biologics Evaluation and Research, terminate the IND. An IND so terminated is subject to reinstatement by the Director on the basis of additional submissions that eliminate such danger. If an IND is terminated under this paragraph, the agency will afford the sponsor an opportunity for a regulatory hearing under part 16 on the question of whether the IND should be reinstated.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11579, Mar. 29, 1990; 57 FR 13249, Apr. 15, 1992]

§312.45 Inactive status.

(a) If no subjects are entered into clinical studies for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, the IND may be placed by FDA on inactive status. This action may be taken by FDA either on request of the sponsor or on FDA's own initiative. If FDA seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. Upon receipt of such notification, the sponsor shall have 30 days to respond as to why the IND should continue to remain active.

(b) If an IND is placed on inactive status, all investigators shall be so notified and all stocks of the drug shall be returned or otherwise disposed of in accordance with §312.59.

(c) A sponsor is not required to submit annual reports to an IND on inactive status. An inactive IND is, however, still in effect for purposes of the public disclosure of data and information under §312.130.

(d) A sponsor who intends to resume clinical investigation under an IND placed on inactive status shall submit a protocol amendment under §312.30 containing the proposed general investigational plan for the coming year and appropriate protocols. If the protocol amendment relies on information previously submitted, the plan shall reference such information. Additional information supporting the proposed investigation, if any, shall be submitted in an information amendment. Notwithstanding the provisions of §312.30, clinical investigations under an IND on inactive status may only resume (1) 30 days after FDA receives the protocol amendment, unless FDA notifies the sponsor that the investigations described in the amendment are subject to a clinical hold under §312.42, or (2) on earlier notification by FDA that the clinical investigations described in the protocol amendment may begin.

(e) An IND that remains on inactive status for 5 years or more may be terminated under §312.44.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

§312.47 Meetings.

(a) *General.* Meetings between a sponsor and the agency are frequently useful in resolving questions and issues raised during the course of a clinical investigation. FDA encourages such meetings to the extent that they aid in the evaluation of the drug and in the solution of scientific problems concerning the drug, to the extent that FDA's resources permit. The general principle underlying the conduct of such meetings is that there should be

free, full, and open communication about any scientific or medical question that may arise during the clinical investigation. These meetings shall be conducted and documented in accordance with part 10.

(b) *"End-of-Phase 2" meetings and meetings held before submission of a marketing application.* At specific times during the drug investigation process, meetings between FDA and a sponsor can be especially helpful in minimizing wasteful expenditures of time and money and thus in speeding the drug development and evaluation process. In particular, FDA has found that meetings at the end of Phase 2 of an investigation (end-of-Phase 2 meetings) are of considerable assistance in planning later studies and that meetings held near completion of Phase 3 and before submission of a marketing application ("pre-NDA" meetings) are helpful in developing methods of presentation and submission of data in the marketing application that facilitate review and allow timely FDA response.

(1) *End-of-Phase 2 meetings*—(i) *Purpose.* The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

(ii) *Eligibility for meeting.* While the end-of-Phase 2 meeting is designed primarily for IND's involving new molecular entities or major new uses of marketed drugs, a sponsor of any IND may request and obtain an end-of-Phase 2 meeting.

(iii) *Timing.* To be most useful to the sponsor, end-of-Phase 2 meetings should be held before major commitments of effort and resources to specific Phase 3 tests are made. The scheduling of an end-of-Phase 2 meeting is not, however, intended to delay the transition of an investigation from Phase 2 to Phase 3.

(iv) *Advance information.* At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor's plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies, and, if available, tentative labeling for the drug. The recommended contents of such a submission are described more fully in FDA Staff Manual Guide 4850.7 that is publicly available under FDA's public information regulations in part 20.

(v) *Conduct of meeting.* Arrangements for an end-of-Phase 2 meeting are to be made with the division in FDA's Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research which is responsible for review of the IND. The meeting will be scheduled by FDA at a time convenient to both FDA and the sponsor. Both the sponsor and FDA may bring consultants to the meeting. The meeting should be directed primarily at establishing agreement between FDA and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. The adequacy of the technical information to support Phase 3 studies and/or a marketing application may also be discussed. FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and whether their submission will be deferred until after approval. Agreements reached at the meeting on these matters will be recorded in minutes of the conference that will be taken by FDA in accordance with § 10.65 and provided to the sponsor. The minutes along with any other written material provided to the sponsor will serve as a permanent record of any agreements reached. Barring a significant scientific development that requires otherwise, studies conducted in accordance with the agreement shall be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug.

(2) *"Pre-NDA" and "pre-BLA" meetings.* FDA has found that delays associated with the initial review of a marketing application may be reduced by

exchanges of information about a proposed marketing application. The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. Arrangements for such a meeting are to be initiated by the sponsor with the division responsible for review of the IND. To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:

(i) A brief summary of the clinical studies to be submitted in the application.

(ii) A proposed format for organizing the submission, including methods for presenting the data.

(iii) Information on the status of needed or ongoing pediatric studies.

(iv) Any other information for discussion at the meeting.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11580, Mar. 29, 1990; 63 FR 66669, Dec. 2, 1998]

§312.48 Dispute resolution.

(a) *General.* The Food and Drug Administration is committed to resolving differences between sponsors and FDA reviewing divisions with respect to requirements for IND's as quickly and amicably as possible through the cooperative exchange of information and views.

(b) *Administrative and procedural issues.* When administrative or procedural disputes arise, the sponsor should first attempt to resolve the matter with the division in FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND, beginning with the consumer safety officer assigned to the application. If the dispute is not resolved, the sponsor may raise the matter with the person designated as ombudsman, whose function shall be to investigate what has happened and to facilitate a timely and equitable resolution. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings and obtaining timely replies to inquiries. Further details on this procedure are contained in FDA Staff Manual Guide 4820.7 that is publicly available under FDA's public information regulations in part 20.

(c) *Scientific and medical disputes.* (1) When scientific or medical disputes arise during the drug investigation process, sponsors should discuss the matter directly with the responsible reviewing officials. If necessary, sponsors may request a meeting with the appropriate reviewing officials and management representatives in order to seek a resolution. Requests for such meetings shall be directed to the director of the division in FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

(2) The "end-of-Phase 2" and "pre-NDA" meetings described in §312.47(b) will also provide a timely forum for discussing and resolving scientific and medical issues on which the sponsor disagrees with the agency.

(3) In requesting a meeting designed to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other consultants, as designated by the agency. Applicants may rely on, and may

bring to any meeting, their own consultants. For major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of its standing advisory committees for its consideration and recommendations.

[52 FR 8831, Mar. 19, 1987, as amended at 55 FR 11580, Mar. 29, 1990]

Subpart D—Responsibilities of Sponsors and Investigators

§ 312.50 General responsibilities of sponsors.

Sponsors are responsibile for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

§ 312.52 Transfer of obligations to a contract research organization.

(a) A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.

(b) A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" in this part apply to a contract research organization to the extent that it assumes one or more obligations of the sponsor.

§ 312.53 Selecting investigators and monitors.

(a) *Selecting investigators.* A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.

(b) *Control of drug.* A sponsor shall ship investigational new drugs only to investigators participating in the investigation.

(c) *Obtaining information from the investigator.* Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:

(1) A signed investigator statement (Form FDA–1572) containing:

(i) The name and address of the investigator;

(ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator;

(iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;

(iv) The name and address of any clinical laboratory facilities to be used in the study;

(v) The name and address of the IRB that is responsible for review and approval of the study(ies);

(vi) A commitment by the investigator that he or she:

(*a*) Will 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, the rights, or welfare of subjects;

(*b*) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

(*c*) Will personally conduct or supervise the described investigation(s);

(*d*) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part

50) and institutional review board review and approval (21 CFR part 56) are met:

(*e*) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with §312.64:

(*f*) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

(*g*) Will 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.

(vii) A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

(viii) A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).

(2) *Curriculum vitae.* A curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.

(3) *Clinical protocol.* (i) For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

(ii) For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

(4) *Financial disclosure information.* Sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

(d) *Selecting monitors.* A sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 61 FR 57280, Nov. 5, 1996; 63 FR 5252, Feb. 2, 1998]

§312.54 Emergency research under §50.24 of this chapter.

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under §50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures required by §50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor promptly shall submit to the IND file and to Docket Number 95S–0158 in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857, copies of the information that was disclosed, identified by the IND number.

(b) The sponsor also shall monitor such investigations to identify when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in §50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical investigation, and other IRB's

that are asked to review this or a substantially equivalent investigation.

[61 FR 51530, Oct. 2, 1996]

§ 312.55 Informing investigators.

(a) Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in § 312.23(a)(5).

(b) The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with § 312.32.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

§ 312.56 Review of ongoing investigations.

(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.

(b) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA–1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of § 312.59 and shall notify FDA.

(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under § 312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with § 312.33.

(d) A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall discontinue those investigations that present the risk, notify FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by § 312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a sponsor on the need to discontinue an investigation.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

§ 312.57 Recordkeeping and record retention.

(a) A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

(b) A sponsor shall maintain complete and accurate records showing any financial interest in § 54.4(a)(3)(i), (a)(3)(ii), (a)(3)(iii), and (a)(3)(iv) of this chapter paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to part 54 of this chapter.

(c) A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of

the drug for investigational use is discontinued and FDA has been so notified.

(d) A sponsor shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, §320.38 or §320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in §320.38.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 58 FR 25926, Apr. 28, 1993; 63 FR 5252, Feb. 2, 1998]

§312.58 Inspection of sponsor's records and reports.

(a) *FDA inspection.* A sponsor shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under this part. Upon written request by FDA, the sponsor shall submit the records or reports (or copies of them) to FDA. The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part.

(b) *Controlled substances.* If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying. In addition, the sponsor shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

§312.59 Disposition of unused supply of investigational drug.

The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug in accordance with §312.57.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

§312.60 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, 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. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51530, Oct. 2, 1996]

§312.61 Control of the investigational drug.

An investigator shall administer the drug only to subjects under the investigator's personal supervision or under

the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

§ 312.62 Investigator recordkeeping and record retention.

(a) *Disposition of drug.* An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under § 312.59.

(b) *Case histories.* An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(c) *Record retention.* An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 61 FR 57280, Nov. 5, 1996]

§ 312.64 Investigator reports.

(a) *Progress reports.* The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under § 312.33 to submit annual reports to FDA on the progress of the clinical investigations.

(b) *Safety reports.* An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.

(c) *Final report.* An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

(d) *Financial disclosure reports.* The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 63 FR 5252, Feb. 2, 1998]

§ 312.66 Assurance of IRB review.

An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

§312.68 Inspection of investigator's records and reports.

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to §312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

§312.69 Handling of controlled substances.

If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

§312.70 Disqualification of a clinical investigator.

(a) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has submitted to FDA or to the sponsor false information in any required report, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered but not accepted by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research, the investigator will be given an opportunity for a regulatory hearing under part 16 on the question of whether the investigator is entitled to receive investigational new drugs.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has deliberately or repeatedly submitted false information to FDA or to the sponsor in any required report, the Commissioner will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.

(c) Each IND and each approved application submitted under part 314 containing data reported by an investigator who has been determined to be ineligible to receive investigational drugs will be examined to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the approval of any marketing application.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor who shall have an opportunity for a regulatory hearing under part 16. If a danger to the public health exists, however, the Commissioner shall terminate the IND immediately and notify the sponsor of the determination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be reinstated.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the drug product for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval of the drug product in accordance with the applicable provisions of the act.

(f) An investigator who has been determined to be ineligible to receive investigational drugs may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ investigatioal drugs solely in compliance with the provisions of this part and of parts 50 and 56.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11580, Mar. 29, 1990; 62 FR 46876, Sept. 5, 1997]

Subpart E—Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

AUTHORITY: 21 U.S.C. 351, 352, 353, 355, 371; 42 U.S.C. 262.

SOURCE: 53 FR 41523, Oct. 21, 1988, unless otherwise noted.

§ 312.80 Purpose.

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated §314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedure outlined in this section should be interpreted consistent with that purpose.

§ 312.81 Scope.

This section applies to new drug and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

(a) For purposes of this section, the term "life-threatening" means:

(1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and

(2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival.

(b) For purposes of this section, the term "severely debilitating" means diseases or conditions that cause major irreversible morbidity.

(c) Sponsors are encouraged to consult with FDA on the applicability of these procedures to specific products.

[53 FR 41523, Oct. 21, 1988, as amended at 64 FR 401, Jan. 5, 1999]

§ 312.82 Early consultation.

For products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members. To the extent FDA resources permit, agency reviewing officials will honor requests for such meetings

(a) *Pre-investigational new drug (IND) meetings.* Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) *End-of-phase 1 meetings.* When data from phase 1 clinical testing are available, the sponsor may again request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric studies will be required and whether their submission will be deferred until after approval. The procedures outlined in §312.47(b)(1) with respect to end-of-phase 2 conferences, including documentation of agreements reached, would also be used for end-of-phase 1 meetings.

[53 FR 41523, Oct. 21, 1988, as amended at 63 FR 66669, Dec. 2, 1998]

§312.83 Treatment protocols.

If the preliminary analysis of phase 2 test results appears promising, FDA may ask the sponsor to submit a treatment protocol to be reviewed under the procedures and criteria listed in §§312.34 and 312.35. Such a treatment protocol, if requested and granted, would normally remain in effect while the complete data necessary for a marketing application are being assembled by the sponsor and reviewed by FDA (unless grounds exist for clinical hold of ongoing protocols, as provided in §312.42(b)(3)(ii)).

§312.84 Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.

(a) FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in §312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.

(b) In making decisions on whether to grant marketing approval for products that have been the subject of an end-of-phase 1 meeting under §312.82, FDA will usually seek the advice of outside expert scientific consultants or advisory committees. Upon the filing of such a marketing application under §314.101 or part 601 of this chapter, FDA will notify the members of the relevant standing advisory committee of the application's filing and its availability for review.

(c) If FDA concludes that the data presented are not sufficient for marketing approval, FDA will issue (for a drug) a not approvable letter pursuant to §314.120 of this chapter, or (for a biologic) a deficiencies letter consistent with the biological product licensing procedures. Such letter, in describing the deficiencies in the application, will address why the results of the research design agreed to under §312.82, or in subsequent meetings, have not provided sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

(d) Marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in part 314 or part 600 of this chapter, as well as those in this subpart.

§312.85 Phase 4 studies.

Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain post-marketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

§ 312.86 Focused FDA regulatory research.

At the discretion of the agency, FDA may undertake focused regulatory research on critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation. When initiated, FDA will undertake such research efforts as a means for meeting a public health need in facilitating the development of therapies to treat life-threatening or severely debilitating illnesses.

§ 312.87 Active monitoring of conduct and evaluation of clinical trials.

For drugs covered under this section, the Commissioner and other agency officials will monitor the progress of the conduct and evaluation of clinical trials and be involved in facilitating their appropriate progress.

§ 312.88 Safeguards for patient safety.

All of the safeguards incorporated within parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. This includes the requirements for informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter). These safeguards further include the review of animal studies prior to initial human testing (§ 312.23), and the monitoring of adverse drug experiences through the requirements of IND safety reports (§ 312.32), safety update reports during agency review of a marketing application (§ 314.50 of this chapter), and postmarketing adverse reaction reporting (§ 314.80 of this chapter).

Subpart F—Miscellaneous

§ 312.110 Import and export requirements.

(a) *Imports.* An investigational new drug offered for import into the United States complies with the requirements of this part if it is subject to an IND that is in effect for it under § 312.40 and: (1) The consignee in the United States is the sponsor of the IND; (2) the consignee is a qualified investigator named in the IND; or (3) the consignee is the domestic agent of a foreign sponsor, is responsible for the control and distribution of the investigational drug, and the IND identifies the consignee and describes what, if any, actions the consignee will take with respect to the investigational drug.

(b) *Exports.* An investigational new drug intended for export from the United States complies with the requirements of this part as follows:

(1) If an IND is in effect for the drug under § 312.40 and each person who receives the drug is an investigator named in the application; or

(2) If FDA authorizes shipment of the drug for use in a clinical investigation. Authorization may be obtained as follows:

(i) Through submission to the International Affairs Staff (HFY–50), Associate Commissioner for Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, of a written request from the person that seeks to export the drug. A request must provide adequate information about the drug to satisfy FDA that the drug is appropriate for the proposed investigational use in humans, that the drug will be used for investigational purposes only, and that the drug may be legally used by that consignee in the importing country for the proposed investigational use. The request shall specify the quantity of the drug to be shipped per shipment and the frequency of expected shipments. If FDA authorizes exportation under this paragraph, the agency shall concurrently notify the government of the importing country of such authorization.

(ii) Through submission to the International Affairs Staff (HFY–50), Associate Commissioner for Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, of a formal request from an authorized official of the government of the country to which the drug is proposed to be shipped. A request must specify that the foreign government has adequate information about the drug and the proposed investigational use, that the drug will be used for investigational purposes only, and that the foreign government is satisfied that the drug may legally be used by the intended

consignee in that country. Such a request shall specify the quantity of drug to be shipped per shipment and the frequency of expected shipments.

(iii) Authorization to export an investigational drug under paragraph (b)(2)(i) or (ii) of this section may be revoked by FDA if the agency finds that the conditions underlying its authorization are not longer met.

(3) This paragraph applies only where the drug is to be used for the purpose of clinical investigation.

(4) This paragraph does not apply to the export of new drugs (including biological products, antibiotic drugs, and insulin) approved or authorized for export under section 802 of the act (21 U.S.C. 382) or section 351(h)(1)(A) of the Public Health Service Act (42 U.S.C. 262(h)(1)(A)).

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 64 FR 401, Jan. 5, 1999]

§312.120 Foreign clinical studies not conducted under an IND.

(a) *Introduction.* This section describes the criteria for acceptance by FDA of foreign clinical studies not conducted under an IND. In general, FDA accepts such studies provided they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be utilized to support clinical investigations in the United States and/or marketing approval. Marketing approval of a new drug based solely on foreign clinical data is governed by §314.106.

(b) *Data submissions.* A sponsor who wishes to rely on a foreign clinical study to support an IND or to support an application for marketing approval shall submit to FDA the following information:

(1) A description of the investigator's qualifications;

(2) A description of the research facilities;

(3) A detailed summary of the protocol and results of the study, and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;

(4) A description of the drug substance and drug product used in the study, including a description of components, formulation, specifications, and bioavailability of the specific drug product used in the clinical study, if available; and

(5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under §314.126.

(c) *Conformance with ethical principles.* (1) Foreign clinical research is required to have been conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" (see paragraph (c)(4) of this section) or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual.

(2) For each foreign clinical study submitted under this section, the sponsor shall explain how the research conformed to the ethical principles contained in the "Declaration of Helsinki" or the foreign country's standards, whichever were used. If the foreign country's standards were used, the sponsor shall explain in detail how those standards differ from the "Declaration of Helsinki" and how they offer greater protection.

(3) When the research has been approved by an independent review committee, the sponsor shall submit to FDA documentation of such review and approval, including the names and qualifications of the members of the committee. In this regard, a "review committee" means a committee composed of scientists and, where practicable, individuals who are otherwise qualified (e.g., other health professionals or laymen). The investigator may not vote on any aspect of the review of his or her protocol by a review committee.

(4) The "Declaration of Helsinki" states as follows:

RECOMMENDATIONS GUIDING PHYSICIANS IN BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a

dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 56 FR 22113, May 14, 1991; 64 FR 401, Jan. 5, 1999]

§312.130 Availability for public disclosure of data and information in an IND.

(a) The existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an investigational new drug application for a new drug will be handled in accordance with the provisions established in §314.430 for the confidentiality of data and information in applications submitted in part 314. The availability for public disclosure of all data and information in an investigational new drug application for a biological product will be governed by the provisions of §§601.50 and 601.51.

(c) Notwithstanding the provisions of §314.430, FDA shall disclose upon request to an individual to whom an investigational new drug has been given a copy of any IND safety report relating to the use in the individual.

(d) The availability of information required to be publicly disclosed for investigations involving an exception from informed consent under §50.24 of this chapter will be handled as follows: Persons wishing to request the publicly disclosable information in the IND that was required to be filed in Docket Number 95S–0158 in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857, shall

submit a request under the Freedom of Information Act.

[52 FR 8831, Mar. 19, 1987. Redesignated at 53 FR 41523, Oct. 21, 1988, as amended at 61 FR 51530, Oct. 2, 1996; 64 FR 401, Jan. 5, 1999]

§ 312.140 Address for correspondence.

(a) Except as provided in paragraph (b) of this section, a sponsor shall send an initial IND submission to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, Park Bldg., Rm. 214, 12420 Parklawn Dr., Rockville, MD 20852. On receiving the IND, FDA will inform the sponsor which one of the divisions in the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research is responsible for the IND. Amendments, reports, and other correspondence relating to matters covered by the IND should be directed to the appropriate division. The outside wrapper of each submission shall state what is contained in the submission, for example, "IND Application", "Protocol Amendment", etc.

(b) Applications for the products listed below should be submitted to the Division of Biological Investigational New Drugs (HFB-230), Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892. (1) Products subject to the licensing provisions of the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 *et seq.*)) or subject to part 600; (2) ingredients packaged together with containers intended for the collection, processing, or storage of blood or blood components; (3) urokinase products; (4) plasma volume expanders and hydroxyethyl starch for leukapheresis; and (5) coupled antibodies, i.e., products that consist of an antibody component coupled with a drug or radionuclide component in which both components provide a pharmacological effect but the biological component determines the site of action.

(c) All correspondence relating to biological products for human use which are also radioactive drugs shall be submitted to the Division of Oncology and Radiopharmaceutical Drug Products (HFD–150), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, except that applications for coupled antibodies shall be submitted in accordance with paragraph (b) of this section.

(d) All correspondence relating to export of an investigational drug under § 312.110(b)(2) shall be submitted to the International Affairs Staff (HFY–50), Office of Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11580, Mar. 29, 1990]

§ 312.145 Guidance documents.

(a) FDA has made available guidance documents under § 10.115 of this chapter to help you to comply with certain requirements of this part.

(b) The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) maintain lists of guidance documents that apply to the centers' regulations. The lists are maintained on the Internet and are published annually in the FEDERAL REGISTER. A request for a copy of the CDER list should be directed to the Office of Training and Communications, Division of Communications Management, Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. A request for a copy of the CBER list should be directed to the Office of Communication, Training, and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448.

[65 FR 56479, Sept. 19, 2000]

Subpart G—Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests

§ 312.160 Drugs for investigational use in laboratory research animals or in vitro tests.

(a) *Authorization to ship.* (1)(i) A person may ship a drug intended solely for tests in vitro or in animals used only for laboratory research purposes if it is labeled as follows:

CAUTION: Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans.

(ii) A person may ship a biological product for investigational in vitro diagnostic use that is listed in § 312.2(b)(2)(ii) if it is labeled as follows:

CAUTION: Contains a biological product for investigational in vitro diagnostic tests only.

(2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for tests in vitro or in animals used only for laboratory research.

(3) A person who ships a drug under paragraph (a) of this section shall maintain adequate records showing the name and post office address of the expert to whom the drug is shipped and the date, quantity, and batch or code mark of each shipment and delivery. Records of shipments under paragraph (a)(1)(i) of this section are to be maintained for a period of 2 years after the shipment. Records and reports of data and shipments under paragraph (a)(1)(ii) of this section are to be maintained in accordance with § 312.57(b). The person who ships the drug shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify records required to be maintained under this section.

(b) *Termination of authorization to ship.* FDA may terminate authorization to ship a drug under this section if it finds that:

(1) The sponsor of the investigation has failed to comply with any of the conditions for shipment established under this section; or

(2) The continuance of the investigation is unsafe or otherwise contrary to the public interest or the drug is used for purposes other than bona fide scientific investigation. FDA will notify the person shipping the drug of its finding and invite immediate correction. If correction is not immediately made, the person shall have an opportunity for a regulatory hearing before FDA pursuant to part 16.

(c) *Disposition of unused drug.* The person who ships the drug under paragraph (a) of this section shall assure the return of all unused supplies of the drug from individual investigators whenever the investigation discontinues or the investigation is terminated. The person who ships the drug may authorize in writing alternative disposition of unused supplies of the drug provided this alternative disposition does not expose humans to risks from the drug, either directly or indirectly (e.g., through food-producing animals). The shipper shall maintain records of any alternative disposition.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987. Redesignated at 53 FR 41523, Oct. 21, 1988]

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

Subpart A—General Provisions

Subpart B—Applications

AUTHORITY: 5 U.S.C. 301; 42 U.S.C. 289.

EDITORIAL NOTE: The Department of Health and Human Services issued a notice of waiver regarding the requirements set forth in part 46, relating to protection of human subjects, as they pertain to demonstration projects, approved under section 1115 of the Social Security Act, which test the use of cost—sharing, such as deductibles, copayment and coinsurance, in the Medicaid program. For further information see 47 FR 9208, Mar. 4, 1982.

Subpart A—Basic HHS Policy for Protection of Human Research Subjects

AUTHORITY: 5 U.S.C. 301; 42 U.S.C. 289, 42 U.S.C. 300v-1(b).

SOURCE: 56 FR 28012, 28022, June 18, 1991, unless otherwise noted.

§46.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in §46.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in §46.102(e) must be reviewed and approved, in compliance with §46.101, §46.102, and §46.107 through §46.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that

the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, Department of Health and Human Services (HHS), and shall also publish them in the FEDERAL REGISTER

or in such other manner as provided in department or agency procedures.[1]

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991]

§46.102 Definitions.

(a) *Department or agency head* means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

(b) *Institution* means any public or private entity or agency (including federal, state, and other agencies).

(c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) *Research subject to regulation,* and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily

[1] Institutions with HHS-approved assurances on file will abide by provisions of title 45 CFR part 46 subparts A–D. Some of the other Departments and Agencies have incorporated all provisions of title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, subparts B and C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

life or during the performance of routine physical or psychological examinations or tests.

(j) *Certification* means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

§ 46.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, HHS, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Protection from Research Risks, HHS.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under § 46.101 (b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head, unless in accord with § 46.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, HHS.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to

eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under §46.101 (b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §46.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by §46.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

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[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991]

§§46.104—46.106 [Reserved]

§46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§ 46.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in § 46.103(b)(4) and, to the extent required by, § 46.103(b)(5).

(b) Except when an expedited review procedure is used (see § 46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§ 46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 46.116. The IRB may require that information, in addition to that specifically mentioned in § 46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with § 46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

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§ 46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REGISTER. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, HHS, Bethesda, Maryland 20892.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§46.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or

that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

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§ 46.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

§ 46.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described is § 46.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in § 46.103(b)(4) and § 46.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by § 46.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

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§ 46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) Public benefit of service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to

provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

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§ 46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by § 46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(Approved by the Office of Management and Budget under control number 9999–0020)

§ 46.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under § 46.101 (b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

§ 46.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the

research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

§46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§46.121 [Reserved]

§46.122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§46.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragarph (a) of this section and whether the applicant or the person or persons who would direct or has have directed the scientific and technical aspects of an activity has have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§46.124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

Subpart B—Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

SOURCE: 40 FR 33528, Aug. 8, 1975, unless otherwise noted.

§46.201 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health and Human Services grants and contracts supporting research, development, and related activities involving: (1) The fetus, (2) pregnant women, and (3) human *in vitro* fertilization.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.202 Purpose.

It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

§ 46.203 Definitions.

As used in this subpart:

(a) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) *Pregnancy* encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

(c) *Fetus* means the product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable.

(d) *Viable* as it pertains to the fetus means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a fetus is viable for purposes of this subpart. If a fetus is viable after delivery, it is a premature infant.

(e) *Nonviable fetus* means a fetus *ex utero* which, although living, is not viable.

(f) *Dead fetus* means a fetus *ex utero* which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).

(g) *In vitro fertilization* means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978]

§ 46.204 Ethical Advisory Boards.

(a) One or more Ethical Advisory Boards shall be established by the Secretary. Members of these board(s) shall be so selected that the board(s) will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research scientists, physicians, psychologists, sociologists, educators, lawyers, and ethicists, as well as representatives of the general public. No board member may be a regular, full-time employee of the Department of Health and Human Services.

(b) At the request of the Secretary, the Ethical Advisory Board shall render advice consistent with the policies and requirements of this part as to ethical issues, involving activities covered by this subpart, raised by individual applications or proposals. In addition, upon request by the Secretary, the Board shall render advice as to classes of applications or proposals and general policies, guidelines, and procedures.

(c) A Board may establish, with the approval of the Secretary, classes of applications or proposals which: (1) Must be submitted to the Board, or (2) need not be submitted to the Board. Where the Board so establishes a class of applications or proposals which must be submitted, no application or proposal within the class may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978; 59 FR 28276, June 1, 1994]

§ 46.205 Additional duties of the Institutional Review Boards in connection with activities involving fetuses, pregnant women, or human in vitro fertilization.

(a) In addition to the responsibilities prescribed for Institutional Review Boards under Subpart A of this part,

the applicant's or offeror's Board shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) Determine that all aspects of the activity meet the requirements of this subpart;

(2) Determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made by the applicant or offeror for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the Institutional Review Board or subject advocates in: (i) Overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen);

(3) Carry out such other responsibilities as may be assigned by the Secretary.

(b) No award may be issued until the applicant or offeror has certified to the Secretary that the Institutional Review Board has made the determinations required under paragraph (a) of this section and the Secretary has approved these determinations, as provided in §46.120 of Subpart A of this part.

(c) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been established under Subpart A of this part.

[40 FR 33528, Aug. 8, 1975, as amended at 46 FR 8386, Jan. 26, 1981]

§46.206 General limitations.

(a) No activity to which this subpart is applicable may be undertaken unless:

(1) Appropriate studies on animals and nonpregnant individuals have been completed;

(2) Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.

(3) Individuals engaged in the activity will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and

(4) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

(b) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

[40 FR 33528, Aug. 8, 1975, as amended at 40 FR 51638, Nov. 6, 1975]

§46.207 Activities directed toward pregnant women as subjects.

(a) No pregnant woman may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if: (1) The purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

§46.208 Activities directed toward fetuses in utero as subjects.

(a) No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the particular fetus and the fetus

will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§ 46.209 Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.

(a) Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity covered by this subpart unless:

(1) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

(2) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

(b) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:

(1) Vital functions of the fetus will not be artificially maintained,

(2) Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(c) In the event the fetus *ex utero* is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

(d) An activity permitted under paragraph (a) or (b) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978]

§ 46.210 Activities involving the dead fetus, fetal material, or the placenta.

Activities involving the dead fetus, mascerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

§ 46.211 Modification or waiver of specific requirements.

Upon the request of an applicant or offeror (with the approval of its Institutional Review Board), the Secretary may modify or waive specific requirements of this subpart, with the approval of the Ethical Advisory Board after such opportunity for public comment as the Ethical Advisory Board considers appropriate in the particular instance. In making such decisions, the Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modification or waiver and that such benefits cannot be gained except through a modification or waiver. Any such modifications or waivers will be published as notices in the FEDERAL REGISTER.

Subpart C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

SOURCE: 43 FR 53655, Nov. 16, 1978, unless otherwise noted.

§ 46.301 Applicability.

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health

and Human Services involving prisoners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.302 Purpose.

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§46.303 Definitions.

As used in this subpart:

(a) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) *DHHS* means the Department of Health and Human Services.

(c) *Prisoner* means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(d) *Minimal risk* is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

§46.304 Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

[43 FR 53655, Nov. 16, 1978, as amended at 46 FR 8386, Jan. 26, 1981]

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

(1) The research under review represents one of the categories of research permissible under §46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet

the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§ 46.306 Permitted research involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:

(1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under § 46.305 of this subpart; and

(2) In the judgment of the Secretary the proposed research involves solely the following:

(i) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(ii) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(iii) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology medicine and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or

(iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Subpart D—Additional Protections for Children Involved as Subjects in Research

SOURCE: 48 FR 9818, Mar. 8, 1983, unless otherwise noted.

§ 46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate

circumstances, the Secretary may, under paragraph (e) of §46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of Subpart A are applicable to this subpart.

[48 FR 9818, Mar. 8, 1983; 56 FR 28032, June 18, 1991; 56 FR 29757, June 28, 1991]

§46.402 Definitions.

The definitions in §46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) *Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

(b) *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) *Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) *Parent* means a child's biological or adoptive parent.

(e) *Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§46.404 Research not involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with

those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of § 46.404, § 46.405, or § 46.406 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) That the research in fact satisfies the conditions of § 46.404, § 46.405, or § 46.406, as applicable, or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The research will be conducted in accordance with sound ethical principles;

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408.

§ 46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with § 46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by § 46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under § 46.404 or § 46.405. Where research is covered by §§ 46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in § 46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may

waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, state or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117 of Subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

PART 50—U.S. EXCHANGE VISITOR PROGRAM—REQUEST FOR WAIVER OF THE TWO-YEAR FOREIGN RESIDENCE REQUIREMENT

Sec.

AUTHORITY: 75 Stat. 527 (22 U.S.C. 2451 et seq.); 84 Stat. 116 (8 U.S.C. 1182(e)).

SOURCE: 49 FR 9900, Mar. 16, 1984, unless otherwise noted.

§50.1 Authority.

Under the authority of Mutual Educational and Cultural Exchange Act of 1961 (75 Stat. 527) and the Immigration and Nationality Act as amended (84 Stat. 116), the Department of Health and Human Services is an "interested United States Government agency" with the authority to request the United States Information Agency to recommend to the Attorney General waiver of the two-year foreign residence requirement for exchange visitors under the Mutual Educational and Cultural Exchange Program.

§50.2 Exchange Visitor Waiver Review Board.

(a) *Establishment.* The Exchange Visitor Waiver Review Board is established to carry out the Department's responsibilities under the Exchange Visitor Program.

(b) *Functions.* The Exchange Visitor Waiver Review Board is responsible for making thorough and equitable evaluations of applications submitted by institutions, acting on behalf of exchange visitors, to the Department of HHS for a favorable recommendation to the United States Information Agency that the two-year foreign residence requirement for exchange visitors under the Exchanges Visitor Program be waived.

(c) *Membership.* The Exchange Visitor Waiver Review Board consists of no fewer than three members and two alternates, of whom no fewer than three

Appendix B
FDA FORMS

Form 1571: Investigational New Drug Application

Form 1572: Statement of Investigator

MEDWATCH Adverse Event Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: September 30, 2002
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR	2. DATE OF SUBMISSION
3. ADDRESS *(Number, Street, City, State and Zip Code)*	4. TELEPHONE NUMBER *(Include Area Code)*
5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*	6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____
(Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
— — —

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

Created by: PSC Media Arts Branch (301) 443-2454 EF

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
5516 Nicholson Lane
Kensington, MD 20895

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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: September 30, 2002.
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

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☐ 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.

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

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8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

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.

I agree to personally conduct or supervise the described investigation(s).

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.

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.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

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.

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.

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.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE

(**WARNING:** A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
5516 Nicholson Lane
Kensington, MD 20895

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ____ of ____

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

FDA Use Only

Triage unit sequence #

A. Patient information

1. **Patient identifier** — In confidence

2. **Age at time of event:** or **Date of birth:**

3. **Sex** ☐ female ☐ male

4. **Weight** ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ **Adverse event** and/or ☐ **Product problem** (e.g., defects/malfunctions)

2. **Outcomes attributed to adverse event** (check all that apply)
- ☐ death ____ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization – initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. **Date of event** (mo/day/yr)

4. **Date of this report** (mo/day/yr)

5. **Describe event or problem**

6. **Relevant tests/laboratory data,** including dates

7. **Other relevant history, including preexisting medical conditions** (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. **Name** (give labeled strength & mfr/labeler, if known)
#1
#2

2. **Dose, frequency & route used**
#1
#2

3. **Therapy dates** (if unknown, give duration) from/to (or best estimate)
#1
#2

4. **Diagnosis for use** (indication)
#1
#2

5. **Event abated after use stopped or dose reduced**
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. **Lot #** (if known)
#1
#2

7. **Exp. date** (if known)
#1
#2

8. **Event reappeared after reintroduction**
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. **NDC #** (for product problems only)
– –

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

D. Suspect medical device

1. **Brand name**

2. **Type of device**

3. **Manufacturer name & address**

4. **Operator of device**
- ☐ health professional
- ☐ lay user/patient
- ☐ other: ____

5. **Expiration date** (mo/day/yr)

6.
model # ____
catalog # ____
serial # ____
lot # ____
other # ____

7. **If implanted, give date** (mo/day/yr)

8. **If explanted, give date** (mo/day/yr)

9. **Device available for evaluation?** (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. **Name & address**

phone #

2. **Health professional?** ☐ yes ☐ no

3. **Occupation**

4. **Also reported to**
- ☐ manufacturer
- ☐ user facility
- ☐ distributor

5. **If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box.** ☐

PLEASE TYPE OR USE BLACK INK

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

***or* FAX to:** 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 to report by phone or for more information
- 1-800-822-7967 for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

Please Use Address Provided Below – Just Fold In Thirds, Tape and Mail

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE, MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Medical Products Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

Mfr report #

UF/Dist report #

FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. **Patient identifier** In confidence

2. **Age at time of event:** or **Date of birth:**

3. **Sex** ☐ female ☐ male

4. **Weight** ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ **Adverse event** and/or ☐ **Product problem** (e.g., defects/malfunctions)

2. **Outcomes attributed to adverse event** (check all that apply)
   - ☐ death ____ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: ____

3. **Date of event** (mo/day/yr)

4. **Date of this report** (mo/day/yr)

5. **Describe event or problem**

6. **Relevant tests/laboratory data**, including dates

7. **Other relevant history, including preexisting medical conditions** (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. **Name** (give labeled strength & mfr/labeler, if known)
   #1
   #2

2. **Dose, frequency & route used**
   #1
   #2

3. **Therapy dates** (if unknown, give duration) from/to (or best estimate)
   #1
   #2

4. **Diagnosis for use** (indication)
   #1
   #2

5. **Event abated after use stopped or dose reduced**
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply

6. **Lot #** (if known)
   #1
   #2

7. **Exp. date** (if known)
   #1
   #2

8. **Event reappeared after reintroduction**
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply

9. **NDC # –** for product problems only (if known)
   – –

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

D. Suspect medical device

1. **Brand name**

2. **Type of device**

3. **Manufacturer name & address**

4. **Operator of device**
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: ____

5. **Expiration date** (mo/day/yr)

6.
   model # ____
   catalog # ____
   serial # ____
   lot # ____
   other #

7. **If implanted, give date** (mo/day/yr)

8. **If explanted, give date** (mo/day/yr)

9. **Device available for evaluation?** (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

E. Initial reporter

1. **Name & address**

phone #

2. **Health professional?** ☐ yes ☐ no

3. **Occupation**

4. **Initial reporter also sent report to FDA** ☐ yes ☐ no ☐ unk

FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Medication and Device Experience Report
(continued)

Refer to guidelines for specific instructions

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

Page ____ of ____

FDA Use Only

F. For use by user facility/distributor–devices only

1. **Check one**
☐ user facility ☐ distributor

2. **UF/Dist report number**

3. **User facility or distributor name/address**

4. **Contact person**

5. **Phone Number**

6. **Date user facility or distributor became aware of event** (mo/day/yr)

7. **Type of report**
☐ initial
☐ follow-up # ____

8. **Date of this report** (mo/day/yr)

9. **Approximate age of device**

10. **Event problem codes** (refer to coding manual)
patient code ____ – ____ – ____
device code ____ – ____ – ____

11. **Report sent to FDA?**
☐ yes ____ (mo/day/yr)
☐ no

12. **Location where event occurred**
☐ hospital
☐ home
☐ nursing home
☐ outpatient treatment facility
☐ outpatient diagnostic facility
☐ ambulatory surgical facility
☐ other: ____ specify

13. **Report sent to manufacturer?**
☐ yes ____ (mo/day/yr)
☐ no

14. **Manufacturer name/address**

G. All manufacturers

1. **Contact office – name/address** (& mfring site for devices)

2. **Phone number**

3. **Report source** (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other: ____

4. **Date received by manufacturer** (mo/day/yr)

5. (A)NDA # ____
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. **If IND, protocol #**

7. **Type of report** (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☐ periodic
☐ Initial ☐ follow-up # ____

8. **Adverse event term(s)**

9. **Mfr. report number**

H. Device manufacturers only

1. **Type of reportable event**
☐ death
☐ serious injury
☐ malfunction (see guidelines)
☐ other: ____

2. **If follow-up, what type?**
☐ correction
☐ additional information
☐ response to FDA request
☐ device evaluation

3. **Device evaluated by mfr?**
☐ not returned to mfr.
☐ yes ☐ evaluation summary attached
☐ no (attach page to explain why not) or provide code: ____

4. **Device manufacture date** (mo/yr)

5. **Labeled for single use?**
☐ yes ☐ no

6. **Evaluation codes** (refer to coding manual)
method ____ – ____ – ____ – ____
results ____ – ____ – ____ – ____
conclusions ____ – ____ – ____ – ____

7. **If remedial action initiated, check type**
☐ recall
☐ repair
☐ replace
☐ relabeling
☐ other: ____
☐ notification
☐ inspection
☐ patient monitoring
☐ modification/ adjustment

8. **Usage of device**
☐ initial use of device
☐ reuse
☐ unknown

9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:

10. ☐ **Additional manufacturer narrative** and/or 11. ☐ **Corrected data**

Please DO NOT RETURN this form to this address.

Appendix C

PROTECTION OF HUMAN SUBJECTS
DECLARATION OF HELSINKI

U.S. Food and Drug Administration

The World Medical Association *Declaration of Helsinki*

World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, and in Hong Kong in 1989.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The Purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical

research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Appendix D

SAMPLE SCHEDULE OF STUDY VISITS AND EVALUATIONS

SAMPLE SCHEDULE OF STUDY VISITS AND EVALUATIONS

	Screen	Baseline	Day 1	Day 2	Week 1	Week 2	Week 4	Week 6	Off-Study
Informed Consent	x								
Entry Criteria	x								
Medical History	x								
Physical Exam		x							x
Abbreviated Exam					x	x	x	x	
Chest X ray		x					x		x
CBC/differential		x							x
WBC	x		x	x	x	x	x	x	
Hemoglobin	x			x	x	x	x	x	
Platelet Count	x			x	x	x	x	x	
Chemistry Panel		x							x
SGPT	x			x	x	x	x	x	x
Alkaline Phos.				x	x	x	x	x	
BUN				x	x	x	x	x	
Creatinine				x	x	x	x	x	
Urinalysis	x	x		x	x	x	x	x	x
Adverse Event			x	x	x	x	x	x	x
Dispense Drug			x			x	x		
Returned Drug						x	x	x	x

Appendix E

ALGORITHMS

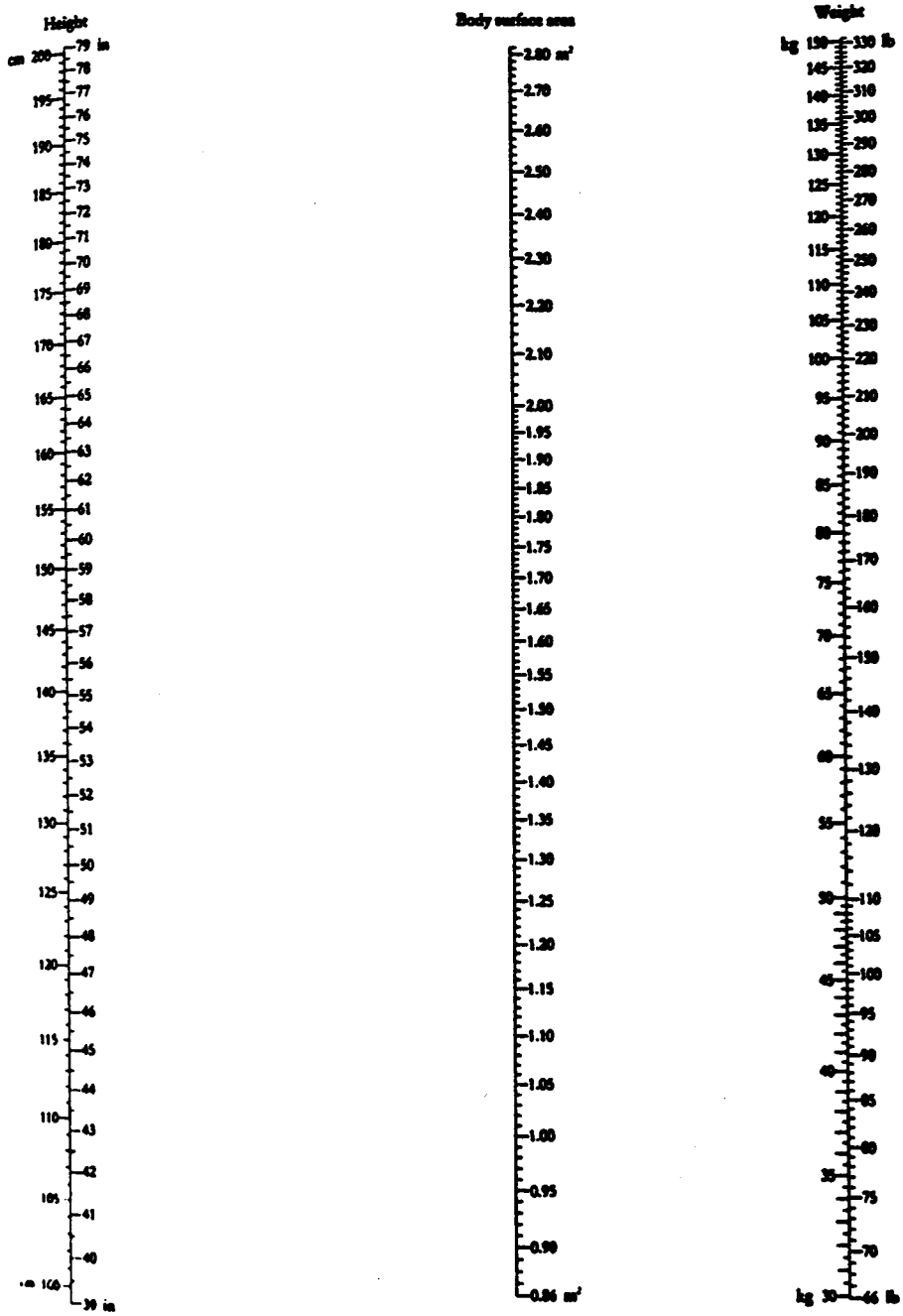
Surface Area

Height/Weight Conversions

Military Time

Temperature Conversion

SURFACE AREA



HEIGHT/WEIGHT CONVERSIONS

HEIGHT:

1 centimeter (cm)	= 0.39 in.
1 inch (in.)	= 2.54 cm

WEIGHT:

1 kilogram (kg)	= 2.2 lb
1 pound (lb)	= 0.4536 kg

HEIGHT CONVERSION TABLE

Height (feet/inches)	Height (inches)	Height (cm)
4' 8"	56	142.2
4' 9"	57	144.8
4' 10"	58	147.3
4' 11"	59	149.9
5' 0"	60	152.4
5' 1"	61	154.9
5' 2"	62	157.5
5' 3"	63	160.0
5' 4"	64	162.6
5' 5"	65	165.1
5' 6"	66	167.6
5' 7"	67	170.2
5' 8"	68	172.7
5' 9"	69	175.3
5' 10"	70	177.8
5' 11"	71	180.3
6' 0"	72	182.9
6' 1"	73	185.4
6' 2"	74	188.0
6' 3"	75	190.5
6' 4"	76	193.0
6' 5"	77	195.6
6' 6"	78	198.1
6' 7"	79	200.7
6' 8"	80	203.2

MILITARY TIME

Military time is based on the 24-hour day, and hours are numbered 1 through 24. The last two digits of military time indicate the minute after the hour. For example, the conventional times 6:30 A.M. and 11:45 P.M. would be written in military time as 0630 and 2345, respectively.

1:00 A.M. = 0100	1:00 P.M. = 1300
2:00 A.M. = 0200	2:00 P.M. = 1400
3:00 A.M. = 0300	3:00 P.M. = 1500
4:00 A.M. = 0400	4:00 P.M. = 1600
5:00 A.M. = 0500	5:00 P.M. = 1700
6:00 A.M. = 0600	6:00 P.M. = 1800
7:00 A.M. = 0700	7:00 P.M. = 1900
8:00 A.M. = 0800	8:00 P.M. = 2000
9:00 A.M. = 0900	9:00 P.M. = 2100
10:00 A.M. = 1000	10:00 P.M. = 2200
11:00 A.M. = 1100	11:00 P.M. = 2300
12:00 A.M. = 1200	12:00 P.M. = 2400

IMPORTANT: Note that 12:00 midnight is written 2400 in military time. However, military time does not exceed 2400 hours. One minute past midnight becomes 0001, thirty minutes past midnight becomes 0030, etc. The time 1:00 A.M. becomes 0100.

TEMPERATURE CONVERSION

To convert Celsius degrees into Fahrenheit, multiply by 9/5 and add 32.

To convert Fahrenheit degrees into Celsius, subtract 32 and multiply by 5/9.

GLOSSARY OF TERMS

ABBREVIATED NEW DRUG APPLICATION (ANDA)

Shortened version of a New Drug Application referencing data from other NDAs.

ACTION LETTER

A letter from the Food and Drug Administration to a sponsor indicating a decision on an application submittal. An *approvable letter* indicates the product can be approved after minor issues are resolved. A *nonapprovable letter* describes significant deficiencies in the application that require correction before the application can be considered.

ACTIVE TREATMENT

A treatment in a clinical trial where an active medication, known to be effective, is used, usually as a positive control compared to the investigational agent.

ADJUVANT

Treatment used in addition to the primary therapy.

ADME

Refers to the absorption, distribution, metabolism, and excretion of a drug compound.

ADMINISTRATIVE LOOK

a. Review of data from an ongoing nonconfirmatory study or

b. Review of data from an ongoing confirmatory trial that is used to make administrative decisions about the design of future trials, allocated manufacturing resources, and so on but NOT to modify the ongoing trial.

ADVERSE DRUG REACTION (ADR), ADVERSE REACTION

See Adverse Experience (AE).

ADVERSE EXPERIENCE (AE)

Any undesirable symptom or occurrence that a trial subject experiences during the clinical trial; it may or may not be considered related to the study agent. *Also referred to as* adverse reaction, adverse event, adverse drug reaction (ADR), and side effect.

ADVISORY COMMITTEE

A committee of outside experts assembled by the Food and Drug Administration (FDA) to review data from a New Drug Application (NDA) submitted to the FDA. The committee consists of experts in the field and meets as needed. Many advisory committees to the FDA exist and differ for different therapeutic areas. The committee does not approve an NDA but only advises the FDA on the merit of the application.

AMENDMENT

to an Investigational New Drug (IND) Application: A change or addition to an IND filed with the Food and Drug Administration; generally, these include a new protocol, a change to an existing protocol, or a new investigator.

to a New Drug Application (NDA): A supplement to a pending NDA, such as a safety update or data obtained from a supplementary study.

to a protocol: A change in a study protocol requiring an amendment to the protocol.

ASCENDING DOSE

Increasingly higher doses of a drug until a maximum tolerated dose (MTD) is reached. These studies are generally Phase I studies.

AUDIT

A careful review of study data, protocol procedures, study conduct, and interim or final study reports to determine whether the conclusions are valid and whether the study has been carried out appropriately.

AUDIT TRAIL

Written record of documents, correspondences, and reports that documents study conduct, such as study files, changes to Case Report Forms, and drug accountability records.

BASELINE

Measurements usually taken at the beginning of a study to serve as a reference for subsequent measurements or observations.

BIAS

Influencing study results by factors other than the treatment being tested.

BIOAVAILABILITY

Determination of amount of drug detectable in blood (or other body tissues) at various times after administration.

BIOEQUIVALENCE

Term used to describe comparable activity of one drug compound to another (usually a generic product to a product that has received approval). If bioequivalence can be demonstrated, the product does not have to undergo extensive clinical trials to demonstrate safety and efficacy.

BIOPHARMACEUTICAL

Refers to pharmaceutical products developed using biotechnology.

BIRA

British Institute of Regulatory Affairs.

BLINDING

Characteristic of a controlled study design to deter bias in interpretation of reported results. In a *double-blind* study, neither the patient nor the investigator knows which treatment the patient receives. In a *single-blind* study, the patient or observer does not know which treatment is being received. In a *triple-blind* study, the investigator, patient, and sponsor all are blinded to the study medication. The term *open study* refers to a trial where all parties may know the treatment the patient receives.

CANDA

Computed-Assisted New Drug Application; a method of filing a New Drug Application with the Food and Drug Administration where much of the information is transmitted electronically.

CASE HISTORY RECORD

The hospital chart, medical office file, or patient record containing medical and demographic information on the study subject. The "source document" used to verify the authenticity of the information recorded in the Case Report Form.

CASE REPORT FORM (CRF)

Form designed specifically for each protocol to collect data on each subject enrolled in a clinical trial. Information collected on the CRF is determined by the study protocol.

CAUSALITY

Relationship between the adverse experience and the test agent in terms defined in the protocol (e.g., not reasonably attributable, possibly attributable, or reasonably attributable).

CBER

Center for Biologics Evaluation and Research, branch of the Food and Drug Administration.

CDER

Center for Drug Evaluation and Research, branch of the Food and Drug Administration.

CDRH

Center for Devices and Radiological Health, branch of the Food and Drug Administration.

CFR

Code of Federal Regulations.

CLINICAL INVESTIGATION

According to Title 21, Part 312.3, of the U.S. Code of Federal Regulations, "means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects."

CLINICAL INVESTIGATOR

See Investigator.

CLINICAL RESEARCH ASSOCIATE (CRA)

A qualified individual working with the sponsor to oversee the progress of a clinical trial; the liaison between the sponsor and the investigator/site. *Also referred to as* Clinical Research Scientist (CRS), Medical Research Associate (MRA), and Monitor.

CLINICAL RESEARCH COORDINATOR (CRC)

Usually a nurse or other health professional, this individual is the study site's organizer of day-to-day conduct of study activities, including completing Case Report Forms, maintaining study files, and assisting the investigator.

CLINICAL STUDY AGREEMENT (CSA)

See Contract.

CLINICAL TRIAL

The systematic investigation of the effects of materials (e.g., investigational drugs, devices) or methods (e.g., surgery, radiation) on a disease state conducted according to a formal study plan (protocol). Generally, a clinical trial refers to the evaluation of treatment methods (drugs, surgery, etc.), although methods of prevention, detection, or diagnosis may also be the objective of a clinical trial.

In the pharmaceutical industry, clinical trials are typically a systematic study of a medicinal product or device in human subjects (patients or nonpatient volunteers) in order to discover or verify the effects of and identify adverse reactions to investigational products in order to ascertain the efficacy and safety of the investigational agents. Also, clinical trials may study the absorption, distribution, metabolism, and excretion as well as the pharmacodynamic interaction of investigational agents.

CLINICAL TRIAL EXEMPTION [CT(X)]

A means of obtaining rapid approval of clinical trials by submitting only summary data (chemistry, pharmacology, toxicology, and volunteer studies).

CODE BREAKER

A sealed envelope or label that contains the identity of the test agent for each study subject; should be opened only under emergency or unusual circumstances, as specified by the protocol and/or the study sponsor.

COINVESTIGATOR/SUBINVESTIGATOR

A physician or qualified individual who assists the Primary Investigator in the conduct of the clinical trial; listed under item 6 of the FDA Statement of Investigator (Form FDA 1572). *Subinvestigator* is the preferred term.

COMBINATION THERAPY

The use of two or more modes of treatment—e.g., surgery, radiotherapy, drug therapy—in combination, alternately or together, to treat a disease.

COMPASSIONATE USE

Circumstances under which certain Food and Drug Administration regulations may be exempt to allow the use of an investigational agent for a single patient.

COMPLIANCE

Patient: A term referring to the degree to which the patient has followed the instructions and dosing requirements of the protocol.

Protocol: Refers to adherence to the procedures defined in the study protocol.

CONFIRMATORY STUDY

Any clinical study designed to provide the substantial evidence of efficacy required for regulatory approval. These studies are typically double blind with a randomized control group.

CONTRACT (Clinical Study Agreement [CSA], Clinical Trial Agreement [CTA])

A document signed and dated by the investigator (or institution representative) and sponsor representative that delineates agreements on financial matters and delegation/ distribution of responsibilities.

CONTRACT RESEARCH ORGANIZATION (CRO)

An independent organization that contracts with the sponsor to assume some of the sponsor's responsibilities for conducting clinical trials. According to Title 21, Part 312.3, of the U.S. Code of Federal Regulations, "means a person that assumes, as an independent contractor with the sponsor, one or more obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration."

CONTRAINDICATION

An indication or condition in which it is recommended that a drug NOT be administered.

CONTROL GROUP

The group of patients receiving the standard treatment or placebo used for comparison to results obtained in the "treatment group," the group of patients undergoing the experimental treatment regimen.

CONTROLLED CLINICAL TRIAL

A study design that compares the investigational drug with either placebo or with another treatment known to be effective against the disease in which subjects are randomly allocated to treatment groups.

COORDINATING CENTER

A clinical research site that will coordinate activities and data management in multi-center trials.

COORDINATING INVESTIGATOR

Investigator assigned to coordinate other investigators at different study sites in a multi-center trial.

CROSSOVER DESIGN

A study design that has each patient participate in two or more treatments in a specified order.

CURRICULUM VITAE (CV)

Prepared by an investigator to summarize his/her training and expertise; similar to a resume.

DATA

Information obtained from a clinical trial, usually recorded on a Case Report Form (CRF) or clinical lab electronic file.

DATA AND SAFETY MONITORING BOARD (DSMB)

An independent group that will review data from ongoing blinded clinical trials to evaluate excessive risk or profound efficacy. The DSMB can stop the clinical trial for excessive toxicity or if evidence is adequate to show treatment is beneficial. *Also called* IDMC, Independent Data Monitoring Committee.

DATA AUDIT

Comparison of source documentation of original data to the data transcribed on a Case Report Form as a check for discrepancies.

DATA EDIT

Comparison of data, manually or automated, to detect incorrect information for the purpose of clarification and quality control of the database.

DATA MANAGEMENT

All data-processing activities, automated and manual, beginning with data collection and transcription through the generation of tables and charts.

DECLARATION OF HELSINKI

See Helsinki, Declaration of.

DHHS

Department of Health and Human Services.

DOCUMENTATION

All records in any form (documents, electronic files, and optical records) describing methods and conduct of a clinical trial, as well as factors affecting the trial and action taken.

DOSE–LIMITING TOXICITY

A dose at which the level of toxicity is a factor in determining dose modifications.

DOSE–RANGING STUDIES

A study design to evaluate the effect and/or safety of different doses of an investigational agent.

DOUBLE BLIND

See Blinding.

DROPOUT

A subject who does not complete all of the protocol-required parameters for a clinical trial.

DSMB

Data and Safety Monitoring Board.

EC

European Community.

EFFICACY

A measure of a drug's ability to ameliorate the signs and/or symptoms of a disease.

EFPIA

European Federation of Pharmaceutical Industries and Associations.

EMEA

European Agency for the Evaluation of Medicinal Products.

ENDPOINT

A predetermined event (per protocol) that indicates a patient's completion of the trial, either by disease state (cure, progression) or by completion of all study visits.

ETHICS COMMITTEE (EC)

An independent group of medical and nonmedical professionals whose purpose is to verify that the clinical trial is performed safely, with integrity, and with respect to the rights of the human subjects. Most countries require that an EC provide a statement of its opinion on any research involving human subjects. The Ethics Committee is the European Union equivalent of the U.S. Institutional Review Board.

EU

European Union.

EVALUABLE PATIENT

Patient in a clinical trial who has satisfied all protocol requirements and may be evaluated for safety and efficacy in the analysis.

FINAL REPORT (by Investigator)

Each investigator is required to summarize the clinical trial (per specifications of their Institutional Review Board [IRB]) and submit it to the IRB and sponsor in a final report.

FINAL STUDY REPORT (*or* Final Medical Report)

A complete and comprehensive description of the completed study, including descriptions of experimental materials and methods, presentation and evaluation of the results, statistical analyses, and a critical discussion of the results.

FOOD AND DRUG ADMINISTRATION (FDA)

The federal agency responsible for regulating the sale of food, drugs, and cosmetics in the United States.

GOOD CLINICAL PRACTICE (GCP)

A standard by which clinical trials are designed, implemented, and reported to assure that the data are scientifically sound and that the rights of the subjects are protected. Refer to Title 21, Parts 50, 56, 312, 314, 600, 601, 812, and 813 of the U.S. Code of Federal Regulations.

GOOD LABORATORY PRACTICE (GLP)

Regulations pertaining to research laboratories. Refer to Title 21, Part 58, of the U.S. Code of Federal Regulations.

GOOD MANUFACTURING PRACTICE (GMP)

That part of pharmaceutical quality assurance that ensures that products are consistently produced and controlled in conformity with quality standards appropriate for their intended use and as required by the product specification. Refer to Title 21, Part 211, of the U.S. Code of Federal Regulations.

HELSINKI, DECLARATION OF

International document concerning the ethical conduct of clinical trials.

ICH

International Conference on Harmonisation.

IDE

Investigational Device Exemption.

IDMC

See Data and Safety Monitoring Board.

INDEMNIFICATION

A legal document indicating protection or exemption from liability for compensation or damages from a third party; usually protects an investigator and/or hospital or institution from claims made by the study subject (or relatives) that harm was caused to the subject as a result of participation in the clinical trial.

INDICATION

The disease state or medical problem being evaluated with the study agent.

INFORMATION AMENDMENT

Refers to an amendment to the Investigational New Drug Application (not necessarily to a specific protocol) that provides additional information, such as the addition of a new investigator.

INFORMED CONSENT FORM

Form used to confirm a trial subject's willingness to participate voluntarily in a study. The subject or legal representative signs the form after all appropriate information about the trial, including objectives, potential benefits and risks, and subject rights and responsibilities, has been explained and all subject questions have been answered. The Informed Consent Form and information must be reviewed and approved by the Institutional Review Board.

INSPECTION

An official audit conducted by regulatory authorities of the Food and Drug Administration, sponsor, or cooperative group at the site of investigation and/or the sponsor. The purpose of the inspection is to verify adherence to applicable regulations and guidelines, including those of Good Clinical Practice.

INSTITUTIONAL REVIEW BOARD (IRB)

An independent body of medical and nonmedical members established according to requirements outlined in Title 21, Part 56, of the U.S. Code of Federal Regulations. The IRB, usually institution specific, is responsible for the initial and continuing approval of research involving human subjects, as well as for verifying the protection of safety and rights of those human subjects.

INVESTIGATIONAL AGENT OR PRODUCT

A pharmaceutical product, placebo, or device being used in an investigational clinical trial.

INVESTIGATIONAL NEW DRUG

According to Title 21, Part 312.2, of the U.S. Code of Federal Regulations, "means a new drug, antibiotic drug, or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes."

INVESTIGATIONAL NEW DRUG (IND) APPLICATION

In the United States, process by which investigational new drugs are registered with the Food and Drug Administration for administration to human subjects in clinical trials; includes information on pharmacology, chemistry, toxicology, previous clinical studies results, and future study proposals.

INVESTIGATOR (Principal Investigator)

As the leader of the investigational team, this individual (usually a physician or dentist) is responsible for conducting the clinical trial and ensuring the safety and welfare of the study subjects. The investigator signs the Statement of Investigator Form (Form FDA 1572). According to Title 21, Part 312.3, of the U.S. Code of Federal Regulations, "means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or 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. "Subinvestigator" includes any other member of that team."

INVESTIGATOR'S BROCHURE

Collection of all relevant information on the investigational product known prior to the start of a particular clinical trial, including preclinical data such as chemical, pharmaceutical, toxicological; pharmacokinetic and pharmacodymamic data in animals and in man; and the results of earlier clinical trials. The data should support the justification for the proposed trial and evaluate safety or precautions. The brochure should be updated on a continual basis as new information is gathered.

LABORATORY CERTIFICATION

A certificate given to a laboratory indicating that the laboratory is capable of performing all tests as required by use of a proficiency testing program. The certification is usually renewed on a biannual or annual basis after appropriate inspection and testing.

MARKETING AUTHORIZATION APPLICATION (MAA)

A complete dossier of information, including chemical, pharmaceutical, biological, and clinical data, which is sent to a regulatory authority to support a request for marketing authorization in the European Union.

MAXIMUM TOLERATED DOSE (MTD)

The dose determined to be the highest dose to give subjects without unacceptable side effects.

MONITOR

See Clinical Research Associate (CRA).

MONITORING

A contact by the sponsor with an investigator or member of the investigative staff that serves to further the progress of a clinical trial.

MOU

Memo of Understanding. A document between the Food and Drug Administration and other regulatory agencies that allows mutual inspection.

MULTICENTER TRIAL

A clinical trial conducted according to a single protocol at various investigational sites by various investigators.

NEW DRUG APPLICATION (NDA)

The complete dossier of information submitted to the Food and Drug Administration to request marketing authorization for an investigational agent. The contents include chemical, pharmaceutical, biological, and clinical data.

NEW MOLECULAR ENTITY (NME)
(*also referred to as* New Chemical Entity [NCE])

An active ingredient of a drug preparation that has not been previously marketed in the United States.

NIH

National Institutes of Health. A federal agency under the Department of Health and Human Services that is composed of several institutes and centers dedicated to specific areas of medical and health research.

NONCLINICAL STUDIES

See Preclinical Studies.

OPEN LABEL STUDY

A study in which the treatment schedules, drug treatment, and doses are known to both the investigator and the subject.

OHRP

Office of Human Research Protection.

OUTCOME

A result, condition, or event associated with individual study subjects used to assess efficacy.

PACKAGE INSERT

Refers to the prescribing information supplied with a marketed pharmaceutical product and summarizes known information about dosing, safety, and indications.

PARALLEL STUDY DESIGN

A study design where subjects are randomized to one treatment plan for the duration of the trial (as opposed to "crossover" design).

PATIENT INFORMATION SHEET

European Community equivalent of Informed Consent Form; may also refer to the information provided to subjects prior to signing an Informed Consent Form. *See also* Informed Consent Form. May also refer to instructions to patients for administration of investigational agents.

PHARMACEUTICAL PRODUCT

Any substance or combination of substances that has a therapeutic, prophylactic, or diagnostic purpose intended to modify physiological functions and presented in a dosage form suitable for administration to humans.

PHARMACODYNAMICS (PD)

The science involving the pharmacology of the interaction of drugs in a physiological environment.

PHARMACOKINETICS (PK)

The science involving the absorption, distribution, metabolism, and elimination (ADME) of drugs.

PHARMACOECONOMIC STUDY

The study of a specific treatment in relation to the economic benefits of the treatment.

PHARMACOEPIDEMIOLOGY

The study of the use of drugs in the general population and large numbers of specific group types.

PHARMACOLOGY

The science involving drugs—their sources, appearance, chemistry, actions, and uses.

PHASE I

The first clinical trials conducted after filing an Investigational New Drug Application. Generally aimed at establishing safety, pharmacokinetics, and doses in a small number of normal volunteers. *See also* Title 21, Part 312.21, of the U.S. Code of Federal Regulations.

PHASE II

After Phase I studies, Phase II studies are the first look at efficacy in a given indication. They are usually randomized, tightly controlled studies using a relatively small number of carefully selected patients. *See also* Title 21, Part 312.21, of the U.S. Code of Federal Regulations.

PHASE III

Clinical trials where the number of subjects is expanded and the inclusion criteria are less stringent to gain experience with the investigational agent in a large number of patients. Also, specific patient populations, such as geriatrics and pediatrics, may be investigated. *See also* Title 21, Part 312.21, of the U.S. Code of Federal Regulations.

PHASE IV

Phase IV trials are often referred to as "postmarketing studies" and are done for a variety of reasons: to place the drug in the market, to make marketing claims, or to conduct pharmacoeconomic studies and quality-of-life studies. New formulations of the drug or new indications must be investigated in Phase I/II clinical trials.

PLACEBO

An inactive substance made to appear identical to the test agent in appearance and taste used as a control in clinical studies.

PMA

Premarket Approval Application. Refers to devices and application for marketing.

POSTMARKETING SURVEILLANCE

Monitoring by the sponsor of the use of a drug in the general population after approved for marketing to evaluate adverse events.

PRECLINICAL STUDIES

Studies done prior to human clinical trials and aimed at establishing information about a new drug, such as absorption, distribution, metabolism, elimination, toxicity, and carcinogenicity. Preclinical studies may continue after studies in humans are underway. *Also referred to as* Nonclinical Studies.

PRINCIPAL INVESTIGATOR

See Investigator.

PROTOCOL

A detailed plan for the investigation of an experimental agent, treatment, or procedure. This document explains the background, rationale, and objectives of the trial and specifically outlines the design, methodology, organization, and condition of conducting the study.

PROTOCOL–SPECIFIED (PLANNED) ADMINISTRATIVE LOOK

An administrative look at the data that is planned as an integral part of the protocol.

RANDOMIZATION

A method by which study subjects are assigned to a treatment group to obtain equal, comparable treatment groups.

RANDOMIZATION CODE

Investigational agent randomization to a treatment group by subject number. In addition to indicating the randomization on prepackaged drug for individual subjects, subjects may be randomized to a treatment arm by prerandomized numbers sealed in envelopes or randomization cards.

REGIONAL CLINICAL RESEARCH ASSOCIATE (RCRA)

Monitors located in geographic regions. *See also* Clinical Research Associate (CRA).

RISK–BENEFIT RATIO

The relationship between the risks and benefits of a given treatment or procedure. Institutional Review Boards determine that the risks in a study are reasonable with respect to the potential benefits.

SAFETY

Refers to the evaluation of the safeness of a drug when used in humans. May refer to establishing safety of a new drug in an investigational trial or surveillance of the safety of a marketed drug.

SERIOUS ADVERSE EXPERIENCE (SAE)

Any experience that suggests a significant hazard, contraindication, side effect, or precaution. This includes, but is not limited to, any experience that is fatal, life-threatening, or permanently or significantly disabling, or that requires inpatient hospitalization or prolongation of hospitalization. In addition, congenital anomaly, occurrence of malignancy, and overdose are always regarded as serious.

SIDE EFFECT

See Adverse Experience (AE).

SINGLE BLIND

See Blinding.

SOURCE DATA

See Source Document.

SOURCE DOCUMENT

Trial subject's medical chart, laboratory report, nurses' notes, or any official record documenting original observations or activities. Source documents are used for verification of the data entered on the Case Report Form.

SOURCE DOCUMENT VERIFICATION

Process of assuring the validity and completeness of the data recorded in the Case Report Form (CRF) by comparing the information in the source document to that recorded on the CRF.

SPONSOR

Individual or organization that takes responsibility for initiation, organization, and management of a clinical trial. According to Title 21, Part 312.3, of the U.S. Code of Federal Regulations, "means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, government agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct

an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators."

SPONSOR–INVESTIGATOR

According to Title 21, Part 312.3, of the U.S. Code of Federal Regulations, "means 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 under this part include both those applicable to an investigator and a sponsor."

STAGING

A process for categorizing the extent of disease for enrollment into a clinical trial.

STANDARD OPERATING PROCEDURE

Detailed, written instructions for the management of clinical trials.

STANDARD TREATMENT

The treatment currently being used for an indication and considered to be of proven effectiveness.

STATEMENT OF INVESTIGATOR (SOI) FORM (*also called* Form FDA 1572)

FDA–required document for all clinical trials conducted as part of a U.S. Investigational New Drug (IND) Application to register the investigator to do research for the IND; signed by investigator to indicate his/her acceptance of key responsibilities of the clinical trial; contains information about the trial, investigator(s), and key responsibilities.

STRATA/STRATIFICATION

Subgroup of subjects selected by certain variables usually at baseline.

STUDY ARM

One part, segment, or specific treatment group of a study.

STUDY COORDINATOR

See Clinical Research Coordinator (CRC).

STUDY DRUG

The investigational agent(s) being studied in a particular clinical trial; may be in solid, liquid, or gas (such as anesthetic) form.

STUDY FILES

The files located at the study site that pertain to an investigator's documentation of a clinical trial.

SUBINVESTIGATOR/COINVESTIGATOR

A qualified individual (usually a physician or dentist) who assists the Principal Investigator in the conduct of a clinical trial. *See also* Coinvestigator/Subinvestigator and Investigator (Principal Investigator).

SUBJECT

A human being (patient or nonpatient volunteer) participating in a clinical trial. The subject may be a

a. healthy person volunteering in a trial,
b. person with a condition *unrelated* to the use of the investigational product,
c. person whose condition *is related* to the use of the investigational product, or
d. recipient of the study drug being tested or a control.

According to Title 21, Part 312.3, of the U.S. Code of Federal Regulations, "means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease."

SURROGATE OUTCOME

The use of a test or measurement instead of a clinical event as an outcome of a clinical trial.

TEAR–OFF LABELS

Refers to a specific type of label for investigational agent where a portion of the package label can be torn off and may contain specific information about the investigational agent, e.g., the identity of the randomized code.

THERAPEUTIC

Pertaining to treatment.

TOXICOLOGY

The study of the toxic pharmacology of a compound.

TREATMENT GROUP

Group of patients receiving the experimental treatment regimen.

TREATMENT INVESTIGATIONAL NEW DRUG

A mechanism by which a drug is approved for treatment use and made available to patients before it has been approved by the Food and Drug Administration for sale.

TRIPLE BLIND

See Blinding.

UNCONTROLLED

A study where the investigational treatment is not being compared (by study design) to a concurrent treatment as a control.

UNEXPECTED ADVERSE EXPERIENCE

Defined by Food and Drug Administration regulations as any adverse experience that is *not* identified in nature, severity, or frequency in the current Investigator's Brochure or in the risk information described in the investigational plan or in the current Investigational New Drug Application.

UNPLANNED ADMINISTRATIVE LOOK

An administrative look at data that were not anticipated in the protocol but arose after the trial was begun. Generally, this is done to analyze the data if the drug seems to be extremely effective or toxic. The need for unplanned administrative looks may arise occasionally, but these should be done sparingly since they can interfere with the statistical effectiveness of the results of the trial.

WHO

World Health Organization.