A Clinical Trials Manual from the Duke Clinical Research Institute

LESSONS FROM A HORSE NAMED JIM
SECOND EDITION

MARGARET B. LIU and KATE DAVIS

WILEY-BLACKWELL

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Second Edition

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Principal, Clinical Trials Consulting
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(Formerly Manager of the Monitoring Group at the
Duke Clinical Research Institute, Durham, North Carolina, USA)

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"Somewhere, something incredible is waiting to be known."

Carl Sagan (1934–1996)
American astronomer, astrochemist, and author

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Foreword

From its inception, the Duke Clinical Research Institute (DCRI) has had a mission to develop and share knowledge that improves the care of patients around the world through innovative clinical research. Our interest is in saving patients' lives and improving the quality of their lives by providing their clinicians with the latest information about the best ways to care for them. We strive to accomplish this by designing and conducting clinical trials, registries, and outcomes studies that provide the answers to important medical questions about patient care.

The studies that we do require the dedicated input of hundreds of well-trained site personnel, and this manual is designed to help them learn and stay up-to-date on the regulations and processes that affect clinical research. While the basics are contained here, new information that accumulates over time will become available through the Clinical Trials Networks Best Practices Web site (ctnbestpractices.org), which is a living repository of useful information from some of the most experienced sites in the world.

The publication of the second edition of this manual comes at an important juncture in the history of clinical research. As the flattening of the world as well as advances in information technology make it possible to link individuals and groups in diverse locations in jointly seeking the answers to pressing global health problems, it is critically important to remain vigilant about moral and ethical safeguards for every patient enrolled in a trial. Those who study this manual will be well aware of how to ensure patient safety along with fiscal responsibility, trial efficiency, and research integrity.

This edition was suggested and spearheaded by Margaret (Maggie) Liu, who revised the majority of the original. When she left the DCRI some years ago and moved with her family to Singapore, Maggie became aware of the opportunity to spread the word about well-done clinical research beyond our borders. Duke caught up with her two years ago when the School of Medicine here created a joint Duke-National University of Singapore Graduate Medical School. The moment seemed right to update the manual to reflect changes in the regulations as well as changes in the global conduct of this type of research.

In modifying and updating the manual, Maggie strove not only to make additions and changes that reflected modifications in the regulations but also to increase the depth of the information; thus this edition is both broader and deeper than the first edition. Together, Maggie and Kate Davis, along with a host of experts and editors, attended to each detail to assure that it was complete, correct, and eminently readable. As with the first edition, this one truly represents the joint effort of many DCRI employees and collaborators in the academic, industry, and government worlds.

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Preface

In today's world of clinical research, international trials have become routine and electronic data capture is commonly used. Privacy rules have affected the way we collect data, and there are additional experiences and regulations to consider regarding the protection of human subjects. Despite these changes, however, the basic principles that guide the conduct of clinical trials remain the same. The task before us, then, is to continue to apply these principles in the changing scientific, ethical, and societal contexts of modern medical practice and research.

In the nearly 10 years since we wrote the first edition of *Lessons from a Horse Named Jim*, we have seen a number of changes in our personal lives as well. Margaret (Maggie) had the opportunity to move with her family to Singapore and has lived there for the past 8 years. After returning to the clinical trials arena, Maggie has consulted with hospitals in the Singapore health care clusters to create a clinical research coordinator (CRC) network to facilitate CRC education and training that will support expanded trial work in that country. Kate has remained at the Duke Clinical Research Institute (DCRI), although her daily activities are removed from clinical site activities. However, when Kate is asked to offer insight into a site-related issue, that interaction still remains the most fulfilling aspect of her job. Through Maggie's work in Singapore, she found herself often referring to the first edition of *Jim* and realized that the book could be strengthened by the addition of more in-depth information, while still fulfilling its purpose of serving as an introductory manual for clinical research. In addition, Maggie felt that expanding information beyond North America would be worthwhile. Thus, work began on a second edition.

The overall organization of this second edition remains similar to that of the first. The first half of the manual is organized into chapters that provide the historical framework, rules and regulations, definitions, and necessary oversight regarding clinical trials. The remaining chapters focus on how clinical trials are conducted at investigative sites, with an emphasis on the practical application of information presented in the first half of the book. In this edition, we have included a separate chapter on institutional review boards

(IRBs) and have divided the original chapter on protocols into two separate chapters covering general components of a protocol and how to review a specific protocol that you want to consider conducting at your site. The final chapter of this edition provides an overview of international clinical research and some of the advantages and concerns related to conducting clinical trials in developing countries. We have also included additional forms at the back of the book that you may want to use as examples when you need to develop forms or worksheets for your clinical trials.

As was the case for the first edition, this second edition would not have been possible without the insight of our colleagues. We gathered information from many talented and experienced DCRI employees, as well as from external colleagues with whom we established relationships over the years. Some reviewed chapters while others contributed through brainstorming meetings and hallway discussions.

We would like to thank Linda Wu for the final push of encouragement to begin working on the second edition and for her insightful comments on the first edition. Many colleagues contributed to early versions of this edition, including Benetta Walker and Clare Matti, who patiently helped us better understand the practical application of the regulations; Cheri Janning, Allison Handler, and Pam Tenearts, who explained devices to us; Barb Kuzil, who reviewed adverse event and safety information; Donna Christopher, who provided current information regarding study drug accountability, and Sharon Karnash, who provided insight from her experiences on many topics. Nancy Clapp-Channing helped us think through quality of life issues; Kathy Roach and Kaye Fendt shared their insights on quality assurance; and Carolyn Rugloski offered content suggestions for this edition.

A number of clinical research coordinators who are involved with the Clinical Trials Networks Best Practices (CTNBP) Web site reviewed selected chapters for us; our thanks go to Kim Broadway, Vicki Copeland, Bernadette Druken, Lynne Harris, Kathy Kioussopoulos, Steven Klintworth, Jessica Sides; we also thank Buddy West for organizing CTNBP input.

Singapore colleagues who shared clinical trials insights and experiences include Sujatha Sridhar, Kay Thwe Tun, Belinda Mak, Celine Loke, and Ai Bee Ong, as well as Yang Tong Foo, who provided explanation of Singapore's regulations. Wanda Sutherland gave us information regarding Canadian regulatory requirements, Rakhi Kilaru gave us input on statistics, and Edison Liu shared his insights regarding global health and international trials.

As we finalized chapter content, Wanda Parker, Melissa Cornish, and Barbara Lytle answered our questions in their areas of expertise;

Amanda McMillan provided editing support. Our thanks go also to Lisa Berdan for sharing her insights and writing the epilogue, and to Penny Hodgson, Betsy Reid, and Bob Harrington for supporting the second edition. As we neared our deadlines, Cathi Bodine used her skills and patience to organize the many forms that we include in the text and appendix; Jonathon Cook added his graphic design talent to these forms to enhance the text. Finally, Jonathan McCall contributed his tremendous editing skills so that the second edition would be a much more polished and readable version. We are grateful to everyone for their support – we could not have done it without you.

Margaret B. Liu and Kate Davis

Abbreviations

ACRP	Association of Clinical Research Professionals
ADE	Adverse Drug Experience
ADR	Adverse Drug Reaction
AE	Adverse Event
ARO	Academic Research Organization
BLA	Biologic License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CEC	Clinical Endpoints Committee
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DCF	Data Clarification Form
DHHS	Department of Health and Human Services
DIA	Drug Information Association
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice(s)
GLP	Good Laboratory Practice(s)
GMP	Good Manufacturing Practice(s)
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
IRB	Institutional Review Board/Independent Review Board
IVRS	Interactive Voice Response System/Service
NDA	New Drug Application
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PMA	Premarket Application
PMN	Premarket Notification [510(k)]
PMS	Postmarketing Surveillance
QA	Quality Assurance
QI	Quality Initiative
QOL	Quality of Life
RCT	Randomized Controlled Trial
REB	Research Ethics Board (Canada)
SAE	Serious Adverse Event
SMO	Site Management Organization
SoCRA	Society of Clinical Research Associates
SOP	Standard Operating Procedure
WMA	World Medical Association

1 Lessons from a Horse Named Jim and Other Events in History Affecting the Regulation of Clinical Research

In this Chapter

- Milestones in the history of food and drug safety – from the first food laws to the founding of the FDA to the Privacy Rule

"It had become clear to me that medicine could hardly hope to become a science until . . . qualified men could give themselves to uninterrupted study and investigation. I knew nothing of the cost of research; I did not realize its enormous difficulty; the only thing I saw was the overwhelming and universal need and the infinite promise, world-wide, universal, and eternal."

John D. Rockefeller (1839–1937), American Industrialist and Philanthropist

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The First Clinical Trial?

The Book of Daniel in the Bible describes a comparative trial – in which Daniel experiments with feeding youthful palace servants legumes and porridge rather than the rich meats eaten by the king and his court.

The Result?

"And at the end of ten days their countenances appeared fairer and fatter in flesh than all the children which did eat the portion of the king's meat." (Daniel 1:15 KJV)

From the earliest days of civilization, people have been concerned about the quality, safety, and integrity of foods and medicines. The first known English food law was enacted in 1202 when King John of England proclaimed the **Assize of Bread**, a law prohibiting the adulteration of bread with ingredients such as ground peas or beans.[1] One of the earliest food and drug laws in U.S. history was enacted in 1785, when the state of Massachusetts passed the first general food adulteration law regulating food quality, quantity, and branding.

Since then, many events, often accompanied by tragic outcomes, have raised additional concerns related to food and drug safety. This has led in turn to the creation and adoption of regulations that affect the way we investigate and manufacture new products, including medicines and medical devices. The following are only some of the events and subsequent laws or responses, largely drawn from events in the past 150 years of American history that have shaped and defined how we conduct clinical research of investigational products in the U.S. today, as well as how we currently bring these products to market.

The Jungle by Upton Sinclair

Published in 1906, this novel described the lives of people working in Chicago stockyards and slaughterhouses. Sinclair wrote about poisoned rats being ground up in meat, the slaughter of diseased animals, and chemicals used to disguise the smell of rotten meat. The description of meat factories as unsanitary and rat-infested outraged the public. When the sales of American meat dropped dramatically, meat packing companies lobbied the U.S. federal government to pass legislation for improved meat inspection and certification. Their efforts contributed to the passage of the **Meat Inspection Act** and the **Food and Drugs Act** of 1906.[2]

1848 The first U.S. *federal* regulation dates to this year, when American soldiers died as a result of ingesting adulterated quinine during the Mexican War. In response to these deaths, Congress passed the **Drug Importation Act**, requiring U.S. Customs to perform inspections aimed at stopping the importation of adulterated drugs from overseas.

1901 A horse named Jim was used to prepare an antitoxin for diphtheria. After 13 children who received the antitoxin died, authorities discovered that the horse had developed tetanus, thereby contaminating the antitoxin. This tragedy prompted Congress to pass the **Biologics Control Act of 1902**, giving the government regulatory power over antitoxin and vaccine development.

1906 In the early 1900s, the federal government completed a study about the effect of colored dyes and chemical preservatives on digestion and health. Study results, which showed that certain food preservatives and dyes were poisonous, drew widespread attention and public support for a federal food and drug law and resulted in the **Food and Drugs Act** of 1906. The original **Food and Drugs Act** prohibited interstate commerce of misbranded or adulterated food, drugs, and drinks. The Act also mandated truth-in-labeling, authorizing the federal government (enforced by the Bureau of Chemistry) to monitor food purity and the safety of

medicines. Unfortunately, truth-in-labeling did not prevent companies from making false health claims about their products.

1931 As part of a Congressional effort to provide more thorough regulation of food and drug marketing, the Bureau of Chemistry was reorganized and renamed the Food, Drug, and Insecticide Administration in 1927. A few years later in 1931, it was again renamed, this time to its current title of the **U.S. Food and Drug Administration (FDA)**.

1932 The **Tuskegee Study of Untreated Syphilis in the Negro Male** was initiated under the auspices of the U.S. Public Health Service. Research subjects, many of them poor African-American sharecroppers, included 399 men with latent syphilis and 201 without the disease who served as controls. The men were told that they were being treated for "bad blood" and were not told the purpose of the study. When penicillin became available in the 1950s, treatment was not offered to the men with syphilis. It was not until 1972 – 40 years after this study began – that it became widely known that the study followed the untreated course of syphilis and that subjects were deprived of effective treatment in order not to interrupt the project.[3]

1937 Sulfanilamide, introduced in 1935, was very effective in treating bacterial infections, but the pills were barely palatable. To make the drug easier for patients, especially children, to swallow, a chemist created a liquid solution in which the sulfanilamide was dissolved. Soon after this sulfanilamide product came on the market, there were reports of 107 deaths after patients, mostly children, ingested the medication labeled "elixir of sulfanilamide." It was then discovered that it was not an elixir (by definition an alcohol solution), but a diethylene glycol (antifreeze) solution. The FDA successfully removed the product from the market, not because it proved fatal, but only because it was mislabeled. This incident highlighted the need for assuring drug safety before marketing.[4]

1938 The following year, Congress passed the **Food, Drug, and Cosmetic Act of 1938**. The Act expanded the FDA's role, requiring proof of *safety* of new drugs before marketing, and extended the FDA's control to include cosmetics and medical devices.

1940–45 At the end of World War II, the international community became aware that Nazi medical personnel had conducted medical experiments on non-German civilians and prisoners of war in concentration camps such as Auschwitz and Dachau. These experiments, which were done without the consent of the subjects and had

The Nuremberg Code

1. Voluntary consent is absolutely essential
2. Results must be for the good of society and otherwise unobtainable
3. Trials must be based on animal experiments and knowledge of the natural history of the disease or condition
4. Trials must avoid unnecessary physical and mental suffering
5. Trials must not be conducted if injury or death is expected
6. Risks must be less than the importance of the problem
7. Subjects must be protected from harm or injury
8. Trials must be conducted by qualified people
9. Subjects have the freedom to stop at any time
10. Investigators have an obligation to stop if harm occurs

A Trial Account by Douglas O. Linder

"No trial provides a better basis for understanding the nature and causes of evil than do the Nuremberg trials from 1945 to 1949. Those who come to the trials expecting to find sadistic monsters are generally disappointed. What is shocking about Nuremberg is the ordinariness of the defendants: men who may be good fathers, kind to animals, even unassuming – yet committed unspeakable crimes."[6]

no potential benefit to individual participants, included sterilization and euthanasia, as well as exposure to temperature extremes, simulations of high altitude (with reduced air pressure/oxygen), bacteria, and untested drugs.

1946–47 In 1946, the U.S. convened the Doctors' Trial in Nuremberg, Germany, to try 20 German physicians (as well as three other Nazi officials) accused of participating in the Nazi program to euthanize persons deemed "unworthy of life" (the mentally ill, mentally retarded, or physically disabled) or of conducting experiments on concentration camp prisoners without their consent. During the trial, ten ethical standards were drafted as a method for judging the physicians and scientists who had conducted abusive and sadistic biomedical experiments. These principles, known as the **Nuremberg Code**, became the prototype for future codes intended to assure that research in human subjects would be conducted in an ethical manner. (See the Nuremberg Code in Appendix A.)

> After almost 140 days of proceedings, a verdict was handed down in the Doctors' Trial. A total of 85 witnesses testified and almost 1,500 documents were introduced as evidence. Sixteen of the 23 defendants were found guilty, and seven were executed.[5]

1957–62 Even after the announcement of the Nuremberg Code standards, it remained a common practice for drug manufacturers to send samples of unapproved drugs to physicians for *ad hoc* testing on patients; the physicians would then report the results of these informal tests to the drug manufacturers. Unfortunately patients did not know they were being used as test subjects, but the U.S. government was apprehensive about interfering with the doctor–patient relationship.

One tragic result of this practice occurred in the late 1950s to early 1960s with the drug thalidomide, used in Europe to bring a quick, natural sleep for millions of people, and to give pregnant women relief from morning sickness. The German manufacturer claimed it was non-addictive, caused no hang-over, and was safe for pregnant women. By 1957, thalidomide was sold over-the-counter in Germany and by 1960 it was sold throughout Europe, South America, Canada, and other countries.[7]

To introduce it into the United States, a U.S.-based pharmaceutical company submitted an application to the FDA to market thalidomide. Frances Oldham Kelsey, the FDA medical officer assigned to the case, requested more data to support the drug's

safety. Kelsey was concerned that the chronic toxicity studies had not been conducted for sufficiently long periods, the absorption and excretion data were inadequate, and the clinical reports were not based on the results of well-designed, well-executed studies. Late in 1960, the *British Medical Journal* published a letter regarding cases of peripheral neuritis (painful tingling of the arms and feet) in patients taking thalidomide over a long period of time. Kelsey suspected that a drug that could damage nerves could also affect a developing fetus. Her suspicions were confirmed when European physicians began reporting a growing number of women giving birth to deformed babies. By late 1961, a German pediatrician determined the cause of the deformities to be thalidomide. German health authorities pulled the drug from the market and other countries followed. The U.S. pharmaceutical company withdrew its application to the FDA.[8]

An estimated 10,000 babies in Europe and Africa were born with birth defects, including phocomelia (a defective development of the arms and/or legs in which the hands and feet are attached close to the body) to mothers taking thalidomide. While never approved for marketing in the U.S., thalidomide was being used extensively in research in American women. Until this time, there was no requirement to notify the FDA regarding the investigational use of drugs. Therefore, when the FDA approximated the number of U.S. physicians using thalidomide, the estimate of 40–50 fell far short of the more than 1000 physicians actually using the drug in an investigational setting.

1962 Faced with the devastating effects of physicians prescribing untested thalidomide as well as other informal drug testing practices, Congress passed the **Kefauver-Harris Amendment** to the Food, Drug, and Cosmetic Act. It required manufacturers to provide proof of *efficacy* (effectiveness) and greater proof of safety before marketing a new drug, and required assurances of consent from research subjects. The new laws did not eliminate all problems associated with drug testing, but did put a great deal of pressure on manufacturers to obtain data in a more ethical manner.

1964 The World Medical Association (WMA), made up of and funded by voluntary national medical associations representing physicians from countries around the world, identified a need for worldwide recommendations to guide physicians conducting biomedical research involving human subjects. This idea, first

Frances Oldham Kelsey

"Although pressured by the manufacturer to quickly approve a drug already in widespread use throughout the rest of the world, Kelsey held her ground. When she repeatedly asked for more data and effectively forestalled the approval of thalidomide, Kelsey did more than keep a dangerous drug off the market. She set into motion a series of events that would forever change the way drugs are tested, evaluated, and introduced in America."[9]

Thalidomide Use Today

- In 1998 the FDA approved the use of thalidomide for the treatment of the painful and disfiguring skin lesions of erythema nodosum leprosum, a complication of Hansen disease, commonly known as leprosy.
- In 2006, the FDA approved the use of thalidomide in combination with dexamethasone in the treatment of multiple myeloma. Thalidomide has been shown to slow the growth of myeloma cells and inhibit the growth of new blood vessels that feed the cancer cells.
- The use of thalidomide is carefully supervised to ensure that it is not administered to pregnant women. Clinical trials are still being done to see if thalidomide is useful in the treatment of other diseases.

Declaration of Helsinki: Basic principles in the original declaration

The declaration provided guidelines for the ethical treatment of human research subjects:

- Research must be based on animal experiments
- Research must be conducted only by qualified persons
- Research must be of importance when compared to risks
- Risk and benefits must be assessed before research is conducted
- Subjects must be volunteers and informed

Notable Revisions of the Declaration of Helsinki

1975 – Independent Committee Review of informed consent emphasized

1983 – Obtain consent from minors when possible

1989 – Independent Committee Review clarified

1996 – New sentence regarding use of placebo in studies where no proven diagnostic or therapeutic method exists

2000 – 32 Basic Principles; research with cognitively impaired subjects expanded

2002 – Clarification regarding placebo use in the absence of existing proven therapy

2004 – Statement that subjects should have access to the best proven practice/ treatment at the conclusion of a study

2008 – Revised statements about vulnerable populations; reworded statement regarding access to post-study intervention; provided clarification regarding when use of placebo is ethical; requires all clinical trials to be registered in a public database.

brought to the attention of its Medical Ethics Committee in 1953, was inspired in part by the horrors revealed during the Nuremberg Trials. Years of discussion, research, and revisions finally resulted in the adoption of a document, known as the **Declaration of Helsinki**, at the WMA's 18th Medical Assembly in Helsinki, Finland.[10] The Declaration of Helsinki is prefaced by a binding statement for physicians: "The health of my patient will be my first consideration." The declaration, subsequently amended several times by the WMA, provides guidelines for the ethical treatment of human subjects (see Appendix A). The Helsinki declaration provides a clear distinction between situations where a subject benefits from research participation and one where benefit is not expected, and its basic elements are incorporated into the U.S. Code of Federal Regulations.

1966 In spite of the Nuremberg Code and the Declaration of Helsinki, ethical breaches in human research continued to occur. A series of these breaches, including hepatitis studies involving cognitively impaired, institutionalized children, and studies in which live cancer cells were injected into patients without their permission, were documented in a medical journal by Dr. Henry Beecher in 1966.[11]

1972 The **Tuskegee Study of Untreated Syphilis in the Negro Male** was exposed in a front-page New York Times article and led to a public outcry. The study ended when it became widely known that subjects had been misled and were deprived of effective treatment with penicillin.[12]

1974 In response to the Tuskegee Study and other unethical trials, the **National Research Act** was signed into law, creating the *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*. This committee was created to identify the basic ethical principles on which clinical research should be based. Over the next 5 years, several reports were commissioned to identify principles related to research on fetuses, research involving prisoners, research involving children, institutional review boards, and research involving mentally infirm subjects.

1976 The **Medical Device Amendments** to the Food, Drug, and Cosmetic Act provides exemption from premarket notification, premarket approval, and other controls of the Food, Drug and Cosmetic Act in order to encourage the discovery and development of useful medical devices.

1979 The *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research* issued the **Belmont Report**, a statement of basic ethical principles and guidelines for the protection of human research subjects (see Appendix A). The Belmont Report is a timeless document that contains guiding principles, provides an analytical framework, and helps resolve ethical problems related to clinical research. Three basic principles were identified: 1) *respect for persons*, including respect for the decisions of autonomous individuals and protection of those with diminished autonomy; 2) *beneficence*, or an obligation to do no harm, maximizing possible benefits and minimizing possible harm; and 3) *justic*e, the fair and equal distribution of clinical research burdens and benefits.[13]

1980–81 The FDA and Department of Health and Human Services (DHHS) incorporated the principles set forth in the Belmont Report into laws regarding clinical research. The basic regulations governing the practice of clinical research for investigational drugs were issued in Title 21 of the **Code of Federal Regulations** (CFR). Protection of human research subjects is dealt with in 21 CFR Part 50; 21 CFR Part 56 addresses Institutional Review Boards (IRBs); and 21 CFR Part 312 lists regulations pertaining to an investigational new drug application, general responsibilities of investigators, the control of investigational drugs, record keeping and retention, and assurance of IRB reviews. Some components of 21 CFR were written as early as 1975 and it has continued to be revised and amended.

1983 The **Orphan Drug Act** was passed, enabling the FDA to promote research into, and approval and marketing, of otherwise unprofitable drugs needed to treat rare diseases.

1988 **The Food and Drug Administration Act** made the FDA an agency of the DHHS, with a Commissioner of Food and Drugs appointed by the President of the United States.

1990 Congress passed the **Safe Medical Devices Act**, requiring medical device users such as hospitals and nursing homes to report promptly to the FDA any incidents that reasonably suggest that a medical device caused or contributed to the death, serious illness,

Dr. Henry Knowles Beecher

Beecher was a world-renowned anesthesiologist who made many scientific contributions in his field and developed techniques for quantifying subjective clinical responses such as pain, thirst, and mood. Beecher pioneered the recognition of the placebo effect and was an early advocate for double-blind controlled studies. His 1966 exposé provided 22 examples of unethical research occurring at prestigious institutions by highly funded investigators. Beecher was appalled by the universal nature of these ethical violations and even more outraged by the complacency within the medical community.

The Belmont Report was created in 1979 and gets its name from the Belmont Conference Center, located in the state of Maryland, where the document was drafted. It identifies three fundamental ethical principles for all human subject research – **respect for persons**, **beneficence**, and **justice** – and forms the basis for human research regulations in place today.

or injury of a patient. Device users were also required to establish methods for tracing and locating patients depending on such devices.

1990 In the late 1980s, increasing concern about ethical standards for research at an international level precipitated interest in harmonizing research requirements among nations. This movement was formalized when representatives from Europe, Japan, and the United states met at the **International Conference on Harmonisation** *of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)*. A committee of representatives from participating countries was formed to make recommendations for greater standardization in clinical research, with the goal of reducing or eliminating duplication of testing in various countries. Their objectives included better use of human, animal, and material resources. A secondary aim was the elimination of delays in global drug development while maintaining safeguards on quality, safety, efficacy, and regulatory obligations to protect public health.

1997 The FDA published **ICH E6 Good Clinical Practice: Consolidated Guidance** in the *Federal Register*. Although it is not a regulation, it is an effective guideline that helps ensure the proper conduct of clinical research. When studies in other countries are conducted under these ICH Good Clinical Practice (GCP) guidelines, the data collected may be accepted by the FDA to support an application for marketing a product in the United States.

1997–98 In an effort to increase the number of new drugs and biological products for use in children, the FDA established the **Pediatric Rule**, requiring manufacturers of selected new and previously marketed drug and biological products to conduct additional studies to assess safety and efficacy in children before the product could be marketed.

Also during this time, Congress passed the **Food and Drug Administration Modernization Act (FDAMA) of 1997**, which included a provision to extend marketing exclusivity of a drug for an additional 6 months in exchange for the manufacturer conducting pediatric drug studies. Market exclusivity prevents a competitor from marketing a generic drug during the applicable time period of exclusivity. Until this time, manufacturers had been required to either test drugs in children or include disclaimers for use in children on the drug labels. Many manufacturers took the path of writing pediatric disclaimers rather than conducting trials. This led to a lack of information regarding dosing, safety, and efficacy of drugs used in children, with the ultimate result that 75% of all drugs prescribed for

children had not been tested in that population.[14] The goal of this provision of FDAMA was to provide an incentive for manufacturers to conduct pediatric clinical trials.[15]

1999 An 18-year-old subject in a clinical trial, Jesse Gelsinger, died from multiple-organ failure triggered by the infusion of genetically altered cold viruses intended to treat an inherited liver disorder. Although Gelsinger was fairly healthy when he began the study, he did have ornithine transcarboxylase deficiency (OTCD), a rare but serious disease in which a genetic defect prevents the liver from making an enzyme that breaks down ammonia. Gelsinger volunteered to participate in the study to help scientists identify a cure for his disease; four days after receiving the gene therapy, Gelsinger died. Subsequent investigation into his death revealed irregularities in the informed consent process; in particular, information from pre-clinical trials of the therapy regarding the death of monkeys due to liver failure was not made known to potential subjects. Gelsinger also had an elevated ammonia level at the time of study entry, which some say should have excluded him from study participation. A federal panel charged with overseeing safety in gene transfer trials – the Recombinant DNA Advisory Committee (RAC) – recommended a series of changes to ensure patient protection and fully informed consent in gene therapy trials. One step was the development of a database that would allow gene researchers and the FDA to compare research results.[16]

Another step was to rename the **Office for Human Research Protection (OHRP)**, formerly the Office for Protection from Research Risks (OPRR), and transfer it from the NIH to the Office of the Assistant Secretary of the DHHS. This organizational change expanded the OHRP's role and elevated its stature and effectiveness, placing even stronger emphasis on the protection of human subjects.

2000 The *Standards for Privacy of Individually Identifiable Health Information*, known as the "**Privacy Rule**," was issued by DHHS to implement the requirements of the *Health Insurance Portability and Accountability Act* (**HIPAA**) of 1996. The Privacy Rule established a set of national standards for the protection of health information, its goal being to assure the protection of individuals' health information while allowing the flow of health information needed to provide and promote high-quality health care.[17]

What does the HIPAA Privacy Rule do?

- Gives patients more control over their health information
- Sets boundaries on the use and release of health records
- Establishes safeguards to be used by health care providers and others
- Strikes a balance when public responsibility supports disclosure of some health information, for example, to protect public health
- Enables patients to find out how their health information may be used
- Generally limits the release of information to the minimum information needed for the purpose of the disclosure
- Generally gives patients the right to examine and obtain a copy of their own health records and to request corrections to their health records[18]

What information is protected?

- Information in medical/health care records/case notes
- Conversations between doctors, nurses, and other health care providers regarding an individual's care or treatment
- Information in the health insurers' computer systems
- Billing information at hospitals and clinics

2001 The ***Association for the Accreditation of Human Research Protection Programs (AAHRPP)*** was established in response to public concern about the quality of research and the protection of human subjects. AAHRPP established a program to provide accreditation for institutions that meet established criteria for ethically sound research and the protection of human subjects.

2002 The **Best Pharmaceuticals for Children Act** authorized government spending for pediatric trials to improve the safety and efficacy of patented and off-patent medicines for children. It continued the exclusivity provisions for pediatric drugs as mandated earlier under the FDAMA of 1997.

2003 After lawsuits resulted in a temporary suspension of the *Pediatric Rule* in 2002, the **Pediatric Research Equity Act** was enacted, reinstating provisions of the *Pediatric Rule*, and requiring manufacturers to include pediatric trials in the drug development process for certain drug and biologic products.

2005 In an effort to ensure honest reporting of clinical trials, the International Committee of Medical Journal Editors (ICMJE) initiated a policy requiring investigators to enter clinical trial information in a public registry before beginning patient enrollment. The aim of this policy was to ensure that information about clinical trials was publicly available, thereby preventing selective reporting of positive study results.

2007 The **Food and Drug Administration Amendments Act of 2007** amends the Public Health Service Act to mandate registration and results reporting of applicable clinical trials on *www.ClinicalTrials.gov*, an on-line data bank established in 1999, and to make study results more readily accessible to the public. This legislation also includes a requirement that if an applicable clinical trial is funded by a grant from the Department of Health and Human Services, progress reports must include certification that the responsible party has made all required submissions for the applicable trial to www.ClinicalTrials.gov.[19]

2008 The **NIH Public Access Policy**, enacted as section 218 of the Consolidated Appropriations Act of 2008, requires all investigators who receive NIH funding to submit final peer-reviewed manuscripts accepted for journal publication to PubMed Central, a publicly available Web forum. To provide the public with access to the results of NIH funded research, manuscripts must be available at the PubMed Central Web site within 12 months of publication.[20]

More Scandals and Tragedies

In 2005 South Korean scientist Hwang Woo-Suk faked stem cell research and paid junior colleagues to donate eggs for research.

In 2006 in the UK, a phase I trial of an anti-inflammatory monoclonal antibody (TGN1412) targeted to treat inflammatory diseases such as rheumatoid arthritis and chronic lymphocytic leukemia resulted in severe adverse reactions in all six normal volunteers who received the active drug.

This brief overview documents the origin and implementation of many laws and regulations governing clinical research and human subject protection. However, many of these rules have been created in response to isolated and often tragic events, rather than being based on a prospective plan. While much progress has been made, health care providers and regulators of clinical trials continue to face ethical issues in conducting clinical research. Current challenges include how to manage genetic testing, confidentiality in an electronic era, gene therapy, and stem cell research. The conduct of clinical trials will undoubtedly continue to change as the landscape of science and technology shifts and new events unfold to shape the future of this field.

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2 The Process: Developing New Drugs, Biologics, and Devices

In this Chapter

- How new drugs and biologics are developed
- How new devices are developed
- Regulation after a product goes on the market

"Experience is fallacious and judgment difficult."

Hippocrates (460 – 377 BC), Greek physician, known as the "Father of Medicine"

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

The process of developing new drugs is expensive and lengthy, requiring an average of ten years or longer to move a product from pre-clinical studies to marketing approval; the costs can range up to a billion dollars. Many experimental compounds never make it out of the laboratory; those that do move out of the laboratory often fail testing in animal models; and still others that reach clinical trials in humans may demonstrate toxicity or a lack of efficacy. This means that of all potential compounds tested, only a small percentage reach the market as new drugs. Of every 5000 to 10,000 new compounds identified in laboratory testing, as few as 5 may qualify for testing in humans, of these 5, perhaps 1 may be granted U.S. Food and Drug Administration (FDA) approval for marketing.

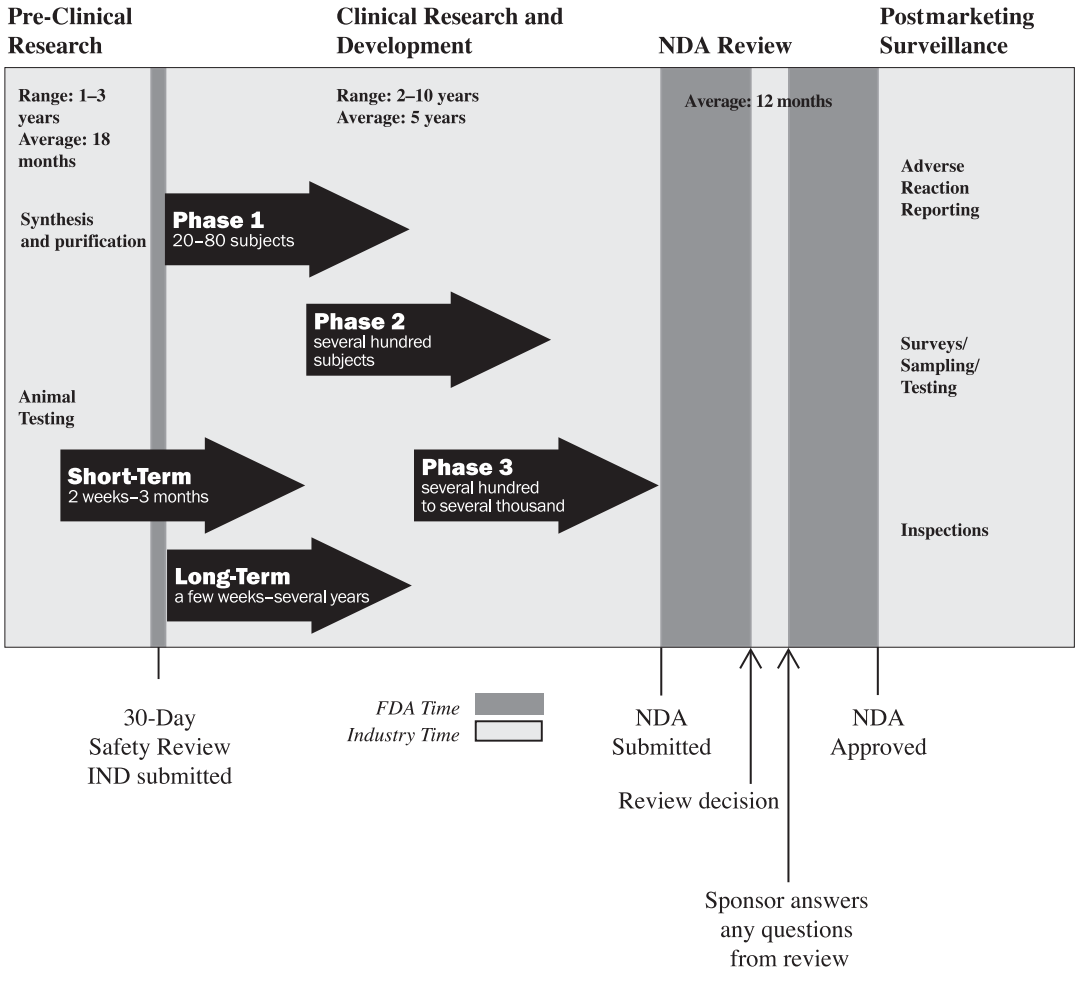
The Drug Development Process

The U.S. approval process for new drugs is designed to be rigorous in order to provide opportunity for a careful and thorough evaluation of the product under investigation. The FDA oversees and monitors the process by setting the appropriate regulations and guidelines to help ensure that only safe and effective products reach the public. To accomplish this, the FDA requires the sponsors of new products to conduct studies in a carefully prescribed manner.

Background Information

The *Pure Food and Drugs Act of 1906* (also known as the "Wiley Act") authorized the U.S. Bureau of Chemistry (a precursor to the FDA) to prevent the marketing of drugs that were adulterated or misbranded. This law only authorized action after marketing and, for an ineffective drug, placed the onus on the federal government to prove that the manufacturer knew their claims of drug effectiveness were false. Recognizing these limitations, Congress passed the *1938 Food, Drug & Cosmetic Act*, which required premarket approval of new drugs, giving the newly-formed FDA authority to review drug *safety* before marketing. In 1962, in response to the scope of the thalidomide tragedy, Congress passed the *Kefauver-Harris Amendment to the Food, Drug & Cosmetic Act* requiring proof of drug *effectiveness* and greater proof of safety before marketing. This amendment changed the drug approval process from one of premarket notification to one of premarket approval, similar to the system in place today.[1]

Figure 2.1 New Drug Development Timeline



Pre-Clinical Studies

When new compounds show potential in laboratory tests, studies are designed to evaluate these compounds for pharmacologic use. These studies of a new compound or drug, generally performed in animals, are referred to as "pre-clinical studies." Pre-clinical studies help establish boundaries for the safe use of the treatment when human testing or "clinical trials" begin. Special care is taken to evaluate the possibility of long-term adverse effects such as the onset of cancer, interference with reproduction, or the induction of birth defects. Many new drugs and treatments are abandoned during pre-clinical studies, having been shown to be unsafe or ineffective in animals.

Development of Rabies Vaccine

In 1885, the great French scientist Louis Pasteur treated two patients who had been exposed to rabies with an experimental anti-rabies vaccine, initially developed in a series of animal studies by Pasteur's colleague Emile Roux. Although Roux's studies of rabies in dogs could qualify as pre-clinical studies in the usual sense, the first use of the vaccine in humans was not done under well-controlled conditions. The first human recipient of the vaccine was a 12-year-old boy (Joseph Meister) who had been badly bitten by a rabid dog. Meister was given the vaccine as a treatment of last resort by Pasteur despite the vehement objection of his partner Roux, who temporarily resigned from Pasteur's group in protest. Meister survived the treatment; some months later, another boy who had been bitten by a rabid dog received the same vaccine and also survived. Pasteur's actions, which were considered extremely risky even by the standards of the day, were initially condemned and he was called upon to explain himself publicly. But because untreated rabies was virtually 100% fatal, it was easy to conclude that the vaccine was effective, and Pasteur was quickly vindicated.[2]

The Investigational New Drug Application

When pre-clinical studies provide sufficient data to warrant study in human subjects, the sponsor of the new product must submit an application to the FDA requesting permission to initiate clinical trials. The application to request permission to begin human testing is commonly referred to as an Investigational New Drug (IND) application, actually a shortened version of the official title of *Notice of Claimed Investigational Exemption for a New Drug*. An IND is not an application for approval but rather an application for exemption from the laws that normally prevent the distribution and use of pharmaceutical agents that have not been given FDA approval. The IND allows the use of an investigational product in human subjects for the sole purpose of conducting clinical trials. The IND application is used for both drugs and biologic products.

Sponsors are required to submit the following components of an IND:

- A completed Form FDA 1571 Investigational New Drug Application.
- Table of contents.
- An introductory statement and general description of the plan for studying the drug or biologic.
- An Investigator's Brochure containing information pertaining to the investigational drug formulation, pharmacokinetics, toxicology, safety and effectiveness from previous studies, and potential anticipated risks and side effects based on prior experience.
- A protocol for each planned study.
- Names of investigators, facilities, and Institutional Review Boards (IRBs) (or completed Forms FDA 1572) where studies will be conducted.
- Chemistry, manufacturing, and control data.
- A summary of previous human experience with the test product, including information acquired if the product was investigated or marketed in another country, or if used in combination with other products previously investigated or marketed.

A complete listing of the required IND content and format can be found in the Code of Federal Regulations (CFR) in 21 CFR 312.23(a)(1–11).

Once the FDA receives an IND application, the FDA has 30 days to review the application before the sponsor can begin clinical testing. If FDA reviewers identify safety concerns, they will issue a "clinical hold," a delay or suspension of the proposed investigations identified in the IND. When the FDA issues a hold, the sponsor is notified by telephone, followed by a letter stating the deficiencies. The clinical trial may not be initiated until the issues or concerns that led to a clinical hold are resolved. This process means that the FDA only issues disapproval (via a clinical hold) of the IND application rather than approval to begin clinical testing. If a sponsor has not heard from the FDA at the end of the 30 days, the sponsor may begin clinical testing as proposed, although most sponsors will contact the FDA if they have not received any notice within the 30-day period.

Clinical Trial Phases

The studies performed under an IND application are often classified into phases, which suggests that the process is made of separate and distinct steps. In practice, however, the phases overlap and trials in one phase are often conducted simultaneously with trials in other phases. In general, clinical trials are classified into the following phases:[4]

Phase 0: Exploratory IND Studies

In 2006 the FDA issued a guidance document regarding exploratory IND studies. To reduce the time and resources spent during early development on products unlikely to succeed, exploratory approaches were identified to enable sponsors more efficient development of promising products while fulfilling regulatory requirements and maintaining human subject protections.

Unlike phase 1 trials, a limited number of doses are administered to fewer subjects in phase 0 trials. Exploratory IND trials include pharmacodynamics (PD) testing (the effects of a drug on the body) and pharmacokinetics (PK) (the activity of a drug in the body over time). Drug and biological products may behave differently in humans than in animals. Phase 0 testing helps to identify this, but the limited human exposure leads to reduced risks because of fewer subjects being exposed to the drug. While there is no intention of therapeutic benefit, subjects are given such low doses of the investigational product that there is usually very little risk.[5]

Form FDA 1571 Statement by the Sponsor

The IND application must include Form FDA 1571 that has been completed and signed by the sponsor. The Form FDA 1571 includes the statements *"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 forth 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."*

Clinical Holds may be issued by the FDA when there is: 1) exposure of human subjects to unreasonable risks of illness or injury; 2) a lack of qualifications of the clinical investigators named in the IND in terms of their training and/or experience; 3) an incomplete or erroneous Investigator's Brochure; 4) deficient design of the plan or protocol in meeting its objectives (for example, if the study of a life-threatening disease affecting both genders excludes men and women with reproductive potential); and 5) insufficient information to assess risk.[3] A complete listing of the grounds for imposing a clinical hold can be found in 21 CFR 312.42(b).

Pharmacodynamics and Pharmacokinetics

Pharmacodynamic (PD) testing describes the biochemical and physiological effects of a drug on the body – how the drug is absorbed, how it moves throughout the body, how it binds to various structures, and how it interacts with molecules within the target tissues.

Pharmacokinetic (PK) testing describes the activity of a drug in the body over a long period of time – the process by which drugs are absorbed, distributed, localized in tissues, and excreted.

PD and PK data are considered together to provide the basis for a rational dosing regimen in phase 1 and phase 2 trials.

Exploratory IND studies can help identify products early in the development process, resulting in fewer human subjects and reduced cost. Because these trials can help identify promising products more quickly and precisely, the use of exploratory IND trials is especially encouraged in the development of products to treat serious or life-threatening diseases.

Phase 0 – Exploratory IND studies:

- are conducted in a limited number of subjects (10–15);
- involve a very small dose;
- have a limited dosing duration (e.g., 7 days);
- have no therapeutic intent;
- are conducted before the traditional phase 1 studies of dose escalation, safety, and tolerance;[6]
- often take less than 6 months to complete.[7]

Phase 1: Evaluation of Clinical Pharmacology and Toxicity

Phase 1 testing is aimed at determining a safe dose range in which a drug or biologic can be administered, the method of absorption and distribution in the body, and possible toxicity. A primary consideration in phase 1 trials is limiting risk to the subjects, and many compounds are abandoned at this stage of testing because of problems with safety or toxicity. Phase 1 studies usually include PK and PD testing to help establish the relationship between drug dose and plasma concentration levels, as well as therapeutic or toxic effects.

Phase 1 trials:

- are conducted to determine the appropriate dose range with regard to safety and toxicity (and if possible, to gain early evidence of effectiveness);
- are used to document human drug metabolism (absorption, distribution, and excretion) and mechanism of action;
- are conducted in a limited number (usually 20–80) of healthy volunteers or patients with a specific disease (such as patients with cancer or AIDS);
- are conducted at only a few locations;
- often take 9–18 months to complete.

Phase 0 and phase 1 studies should be conducted in units that have been set up to ensure careful monitoring and immediate access to facilities for emergency medical treatment. The staff in these units should have medical training and expertise as well as an understanding of the investigational product, its target, and mechanism of action.

Since many first-in-man studies are designed to evaluate investigational product tolerance in healthy volunteers who are not expected to derive any benefit from the product, the rights and safety of the subjects are of primary importance. Protocols for first-in-man studies should be designed to pay particular attention to starting doses and dosing intervals, and allowance made for adequate observation time between doses and subjects. There should be clear stopping rules and a specific plan for identifying and treating adverse events.[8]

Phase 2: Evaluation for Safety and Treatment Effect

Once safety and dosage have been initially identified in phase 1 trials, small-scale, well-controlled phase 2 trials evaluate preliminary safety and efficacy in the targeted population with the specified disease or condition. Determination of a minimum and maximum effective dose (dose-ranging study) and PK data are also components of phase 2 trials. Although there is an emphasis on efficacy, the safety of subjects remains a primary consideration.

Phase 2 trials:

- are conducted in a relatively limited number of subjects (usually 100–300) who have the disease or condition to be treated;
- often involve hospitalized subjects who can be closely monitored;
- may focus on dose-response, dosing schedule, or other issues related to preliminary safety and efficacy;
- often take 1–3 years to complete.

Additional animal testing may also be done simultaneously to obtain long-term safety information. If studies show that the new drug is safe and useful, testing may proceed to phase 3 trials.

Phase 3: Large-Scale Treatment Evaluation

Phase 3 trials involve the most extensive testing to fully assess safety, efficacy, and drug dosage in a large group of subjects with the specific disease to be treated.

Phase 3 trials:

- are conducted in larger and more diverse populations (several hundreds to tens of thousands of subjects) that reflect the patients for whom the drug is ultimately intended;
- make comparisons between the new treatment and standard therapy and/or placebo;
- evaluate the drug in the target patient population, with the drug being administered in the same manner expected to be used by practicing physicians after marketing;
- often take 2–5 years to complete.

Clinical Trial Phases

Phase 0: Exploratory IND studies in limited human subjects

Phase 1: Early stage of testing

Phase 2: Preliminary safety and efficacy studies

- Phase 2a: Pilot trials in selected populations
- Phase 2b: Pivotal trials; most rigorous test of safety

Phase 3: Expanded large-scale studies

- Phase 3b: Trials started after NDA submission but before marketing approval is received

Phase 4: Postmarketing studies (discussed later in this chapter)

With the intention of obtaining additional information regarding the effectiveness and safety data needed to evaluate the overall benefit-risk relationship and long-term safety, phase 3 studies often produce much of the information that is eventually used for package labeling and the package insert.

Trials may be further classified into subsets of phases. For example, phase 2 trials may be divided into phases 2a and 2b. *Phase 2a studies* are pilot trials that evaluate efficacy and safety in selected populations with the disease or condition of interest, while *phase 2b studies* are well-controlled trials that evaluate efficacy and safety (and usually provide the most rigorous demonstration of a drug's safety); phase 2b studies are sometimes referred to as *pivotal trials*.[9] *Phase 3b studies* are trials conducted after a New Drug Application (NDA) has been submitted to the FDA but before approval and marketing. Phase 3b trials may supplement earlier trials or may obtain additional information, such as quality of life or economic information. Phase 3b trials may also be conducted to obtain information for additional indications (e.g., in the pediatric population).

Registries Combined with Phase 3 Trials

Researchers often use disease registries to assess the current status or standard of care for a given medical condition. Registries are designed to include data on all persons who have received a diagnosis of and/or who have been treated for a specific condition. These databases can help researchers understand how care is delivered, as well as the outcomes achieved.

Sometimes registries are combined with phase 3 trials. When prospective subjects choose not to participate in a phase 3 trial, they are often willing to participate in a registry of individuals with the same disease or condition of interest. In this way, researchers can gather data on the disease course and treatment in people outside of the clinical trial and compare them with findings from subjects participating in the study.

Application to Market New Drugs and Biologics

New Drug Application

Once the proposed clinical studies are completed and analyzed and the sponsor believes adequate evidence has been obtained to support a request for marketing approval for the drug, the sponsor submits a

New Drug Application (NDA) to the FDA. The NDA contains extensive data on the test product, results and safety data from the clinical trials conducted, and may include copies of individual subject data forms. Once the FDA receives an NDA, it is distributed to the group of FDA reviewers responsible for the drug or biologics classification. Complete requirements for an NDA submission can be found in 21 CFR Part 314: Applications for FDA Approval to Market a New Drug.

Biologics License Application

As with drugs, biological products ("biologics") are used to treat, prevent, or cure disease in humans. Biologics, as their name suggests, are generally derived from living material – human, animal, or microorganism. Section 351 of the *Public Health Service (PHS) Act* defines a biological product as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." Considered a subset of drugs, biological products are regulated under provisions of the Food, Drug, and Cosmetic Act.

Licensing of biologic products is very similar to the process for approving new drugs. Following laboratory and animal testing that demonstrates investigational use in humans as reasonably safe, clinical trials of biological products in humans can be conducted under an IND – the same application that is used for new drugs – in accordance with the regulations in 21 CFR 312.

If the data show that the biological product is safe and effective for the intended use, they are submitted to CBER (see below) as part of a *Biologics License Application (BLA).* Requirements for a BLA submission can be found in 21 CFR 601.2: Applications for biologics licenses; procedures for filing.

FDA Review Groups

As the agency principally responsible for the safety and efficacy of pharmaceutical agents, biological products, and medical devices produced in the United States, the FDA reviews the clinical research performed and assesses the product's risks, weighing them against the benefits.

CDER and CBER

The following centers within the FDA hold primary responsibility for reviewing and approving or disapproving new drugs and biologics:

1 The *Center for Drug Evaluation and Research* (CDER) has four primary duties: a) reviewing drugs, both prescription and

What is a drug?

CDER regulates drugs used to treat, prevent, or diagnose illnesses. But CDER regulates more than just medicines. Drugs regulated by CDER include fluoride toothpaste, dandruff shampoos, and sunscreens.[10]

What are biologics?

Unlike drugs, which are chemically synthesized, biologics are complex mixtures not easily identified or characterized. They include:

- Allergenics, such as patch tests used to diagnose causes of dermatitis and extracts used to diagnose and treat hay fever, allergic sinusitis, allergic conjunctivitis, and bee stings
- Blood and blood components including red blood cells, platelets, and plasma
- Pharmaceutical products made from blood including immunoglobulins and clotting factors
- Medical devices and tests used to safeguard blood and blood components
- Cellular products, such as human stem cells and pancreatic islet cells
- Gene therapies
- Human tissues, including skin, tendons, ligaments, and cartilage
- Vaccines
- Xenotransplantation products that use live animal cells, tissues, or organs to treat human diseases such as liver failure and diabetes, where human materials are not always available[12]

over-the-counter, before marketing; b) watching for problems, such as unexpected health problems and inadequate supply after drug approval and marketing; c) monitoring drug information for accuracy and truthfulness regarding effectiveness and side effects; and d) protecting drug quality to ensure a safe and effective supply.

2 The *Center for Biologics Evaluation and Research* (CBER) is responsible for blood and blood products, vaccines, allergenics, and biologics. CBER examines blood bank operations and ensures the purity and effectiveness of biological products such as insulin. CBER's regulation of biological products has expanded in recent years to include a wide variety of new products including gene therapies, banked human tissues, and somatic cell stem cell therapies. After marketing approval for a new product, CBER continues to monitor safety of the approved biologics.[11]

FDA Advisory Committees

In addition to FDA review groups such as CDER and CBER, outside reviewers contribute to the review process as members of FDA Advisory Committees. The Advisory Committees may include scientific experts in a specified field, as well as consumer, industry, and patient representatives. In particular, the FDA has a special interest in ensuring adequate representation of women, minorities, and persons with disabilities on Advisory Committees. The primary roles of the Advisory Committees are to provide independent expert scientific advice and to help the FDA make sound decisions about product approval. While the Advisory Committees submit advice and recommendations, the FDA makes the final decisions.

Stem Cell Research

Stem cell research is intended to lead to the development of an infinitely renewable source of cells for cell-replacement therapies to treat disease. **Embryonic stem cells**, derived from 5–7 day old embryos, differ from other cells in the body in that they are both capable of **self-renewal** (i.e., able to divide and renew themselves), and are **pluripotent** (i.e., can differentiate into many kinds of specialized cell types, such as muscle or neuronal tissue). Research into embryonic stem cells seeks to identify precise approaches that would allow scientists to direct stem cell differentiation into specific tissue types, creating a source of tissue for transplantation to replace damaged tissues. Conditions such as Parkinson's disease (see box below), spinal cord injury, muscular dystrophy, heart failure, and diabetes could conceivably be treated using these replacement cells.

Progenitor cells, also called *adult stem cells* or *somatic stem cells*, are isolated from specific bodily tissues. Like embryonic stem cells, they are capable of self-renewal, but can differentiate into only a restricted range of tissues. For example, hematopoietic stem cells can differentiate into red blood cells, white blood cells, and platelets, while pancreatic progenitor cells can differentiate into insulin-secreting islet cells. The primary role of progenitor cells is to replenish the tissue from which they are cultured. Hematopoietic stem cells have been used in bone marrow transplants for the treatment of leukemia. The umbilical cords of newborn infants provide a source of **cord progenitor cells** that have hematopoietic origins.

Stem Cells for the Future Treatment of Parkinson's Disease

Parkinson's disease is a common neurodegenerative disorder that affects more than 2% of the population over 65 years of age. Parkinson's disease is caused by a progressive degeneration and loss of dopamine (DA)-producing neurons in the brain, which leads to tremor, rigidity, and hypokinesia (abnormally decreased mobility). Scientists have been successful in developing methods to induce embryonic stem cells to differentiate into cells with many of the functions of DA neurons, in the hope that these cells can be used for transplantation into patients with Parkinson's disease.[13]

Fast Track Review

The FDA also has an expedited review process – the *fast track* program – for priority drugs and biologics that represent an advance in medical treatment, diagnosis, or disease prevention when compared to marketed products. This program was established after the 1997 enactment of the Food and Drug Administration Modernization Act to shorten the review time of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs.[14] In 2007, the median time required by the FDA to review and approve new drug and

2008 Drug and Biologics Approvals

- 88 NDA/BLA Approvals
- 6 NDA Tentative Approvals under the President's Emergency Plan of AIDS Relief
- Four of the approvals were for biologics
- Of the 88 NDA approvals, 18 underwent fast track/priority review and 4 were designated as orphan drugs (see explanation below)
- Of the 4 biologics approved, 2 were given fast track/priority review and 1 was an orphan product[16]

Priority review and approval was given to difluprednate (trade name Durezol), a topical ophthalmic steroid for the treatment of post-operative ocular inflammatory diseases. Over five million ophthalmic surgeries are performed each year in the United States, and post-operative inflammation is a common occurrence.

One of the **biologics** approved in 2008 was rilonacept (trade name Arcalyst), a product used to treat a spectrum of rare inherited autoinflammatory conditions characterized by spontaneous and environmentally triggered systemic inflammation.

Two of the approved **orphan drugs** in 2008 were tetrabenazine (trade name Xenazine) and bendamustine (trade name Treanda). Tetrabenazine was approved for the treatment of chorea associated with Huntington's disease, characterized by uncoordinated, jerky body movements and a decline in mental abilities. Huntington's chorea affects more than 15,000 Americans and 100,000 people globally. Bendamustine was approved for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL). According to the National Cancer Institute, an estimated 30,000 people in the United States are expected to be diagnosed annually with indolent NHL, a serious and slow-growing cancer of the lymphatic system that is difficult to treat because patients are prone to relapse after treatment.

biologics applications classified as standard review was just over 12 months, while fast track drugs and biologics received a response within approximately 60 days.[15]

Early or Expanded Access to Unapproved Drugs and Biologics

In some situations, drugs or biologics that have not been approved for marketing may be used outside of a clinical trial to save a patient's life or to relieve suffering from a disease with no alternative treatment. A process has been established to make investigational products available in specific circumstances.

Treatment Use of Investigational Drugs

A drug that is not yet approved for marketing may be under clinical investigation for a serious or life-threatening illness in patients for whom there is no comparable or satisfactory alternative. In such cases, a treatment IND may be issued for the purpose of expanding access to promising new drugs for desperately ill patients who are

not participating in the clinical trials. A treatment IND may be issued as early in the drug development process as possible, usually after there are enough data to indicate that the investigational agent may be effective and does not have unreasonable risks.[17] Because safety and side effect data are collected for a treatment IND, the information obtained also contributes to the body of knowledge about the test product.[18]

The requirements to issue a treatment IND are: 1) the drug is intended to treat a serious or immediately life-threatening disease; 2) there is no satisfactory alternative treatment; 3) the drug is under investigation or trials have been completed; and 4) the sponsor is actively pursuing market approval. Treatment INDs require IRB approval and informed consent, although a sponsor can apply for a waiver of IRB review if it can be shown to be in the subject's best interest and if there is a satisfactory alternative method for assuring human subject protection.[19]

Compassionate (Non-Research) Use of Investigational Drugs

There are occasions when a clinical trial has ended and subjects are allowed to continue taking the investigational drug, benefiting from its use while the sponsor pursues marketing approval.[20] This may be referred to as *compassionate use* of an investigational drug.

Compassionate use of a drug may also be granted by the FDA when a drug that has been marketed or is under investigation in another country (but is not available in the U.S.) is the only reasonable and available treatment. Compassionate use has also been approved in cases where a patient does not meet a clinical trial's eligibility criteria, but the drug has the possibility of benefit to the patient, and there is no other treatment available.

Emergency Use of Investigational Drugs

There are times when the need for an investigational drug may arise in an emergency situation in which there is not adequate time to submit an IND. In such a case, the FDA may authorize shipment of the drug for a specific use before an IND is submitted. This authorization is given with the condition that the sponsor will make an IND submission as soon as possible after receiving FDA authorization.[21]

Orphan Drugs

Orphan products are defined as drugs or biologics used to treat rare diseases or conditions that affect fewer than 200,000 persons in the

Difference between Fast Track and Treatment Use of Investigational Drugs/Biologics:

- The fast-track program expedites the process of getting a priority drug or biologic approved for marketing.
- A treatment IND facilitates patient access to drugs/biologic before marketing approval in cases of life-threatening illness.

Family Requests Compassionate Use of Investigational Drug to Treat Son with Muscular Dystrophy

In 2008, the parents of a 16-year old boy with Duchenne muscular dystrophy (an often-fatal genetic degenerative disease) asked the manufacturer of an investigational drug to give their son access to the drug through a "compassionate use" single-patient study. Their son did not meet the eligibility criteria for an ongoing study and even though the FDA had agreed to fast-track the drug, approval was not likely before 2011. The parents were afraid their son, who had lost the ability to walk in the previous year, would not live until FDA approval was granted unless allowed compassionate use of the drug.

Orphan Drugs

A few of the diseases and conditions for which orphan drugs have been approved include:

- idiopathic pulmonary fibrosis;
- cystic fibrosis;
- chronic myelogenous leukemia;
- malignant glioma;
- pancreatic cancer.

Orphan Drug Approval Using Fast Track Designation

In December 2007 – the FDA approved sapropterin (trade name Kuvan), the first drug of its kind approved to slow the effects of a rare genetic disorder that causes mental retardation, smaller brain size, delayed speech and other neurological problems. This disorder, tetrahydrobiopterin (BH4)-responsive phenylketonuria – or PKU disease – occurs in one out of every 12,000 to 15,000 live births in the United States.

"This new drug therapy represents hope for patients and families dealing with this difficult disease," said Janet Woodcock, M.D., FDA's deputy commissioner for scientific and medical programs, chief medical officer, and acting director of the CDER. "Now, for the first time, there is a medical intervention to help patients and their families slow the devastating neurological effects of this disease." Sapropterin was first granted *orphan drug designation* by the FDA in January 2004; 2 years later, it was granted a *fast track designation* by the FDA based on its potential to offer a significant advantage to patients over the current treatment options. The sapropterin NDA also received a priority review by the FDA.[25]

United States.[22] In reality, most of these conditions occur in far fewer patients than this, with almost half of the conditions on the orphan drug list affecting 25,000 or fewer people. These small patient populations make it difficult for a sponsor to profit from the marketing of the drug or biologic, so there has been little incentive for pharmaceutical companies to develop products in these areas.

To encourage manufacturers to develop drugs for rare diseases or conditions, Congress passed the ***Orphan Drug Act*** of 1983 granting special privileges and marketing incentives. The passage of this act gave research groups and drug companies a financial interest in developing and adopting orphan drugs and – equally importantly – focused public, government, and industry attention on the plight of those who suffer from rare diseases. The Act provides annual grant money ($14 million for 2008) to support the development of orphan drugs, allows for FDA support in protocol development and study design, provides tax credits for up to 50% of the cost of clinical trials, waives the Prescription Drug User Act filing fees (approximately $1,000,000 per application in 2008), and gives the sponsor of an orphan drug exclusive marketing rights for 7 years after drug approval.[23]

The *Orphan Drug Act* has had a significant impact on the development of drugs for rare diseases. In the 25 years since its enactment in 1983, more than 325 treatments have been granted FDA approval. This is in direct contrast to the 10 years preceding enactment, when only 10 treatments were developed for rare diseases.[24]

Developing New Devices

There are obvious differences in drugs and devices based on their physical properties and distinctions. For example, it may be relatively easy to visualize and document the performance of a device after use or implantation, but more difficult to determine a drug's performance and effectiveness. Conversely, the technique and skill of the surgeon play a major role in determining whether or not a device implantation is successful, whereas this is not the case for drugs and biologics.

Because of these differences, the process and accompanying regulations for developing devices differs from those that apply to new drugs and biologics, although there are a number of regulations that apply to both drugs and devices, including informed consent and IRB regulations (21 CFR 50 and §56), as well as financial disclosure regulations (21 CFR 54). The goal of device regulations in 21 CFR 800 is to establish a reasonable assurance of safety and effectiveness of medical devices marketed in the United States.

Background Information

Prior to the 1938 Food, Drug & Cosmetic Act the modern device industry could not yet be said to exist; accordingly, there was no regulation of medical instruments. Instruments supplied to doctors and dentists were considered to carry no significant risks to patients. While the 1938 Act gave the FDA jurisdiction over medical devices for the first time, it limited the FDA to challenging the sale of unsafe and ineffective devices. When the 1960s brought a dramatic increase in the number of new medical devices, the FDA became aware of the need for premarket review. Using a broad interpretation of the definition of "drug" in the regulations, the FDA categorized some new devices as drugs, subjecting them to the same review for safety and effectiveness before marketing. For example, the FDA claimed that certain contact lenses were drugs, as well as claiming the Copper-7 (trade name Gravigard) intrauterine device to be a drug because of the chemical action of the copper in the body.

It became clear, however, that classifying devices as drugs was not an appropriate long-term solution to obtaining premarket approval for devices. This realization led to the *1976 Medical Device Amendments* to the Food, Drug & Cosmetic Act. The amendments in this Act:

- required devices to be classified into one of three classes based on risk;
- allowed for the comparison of new devices to ones marketed before the 1976 date of the amendments (evaluating for substantial equivalence);
- established premarket notification [510(k)] to distinguish between pre- and post-amendment devices;
- required premarket approval for new devices determined not to be substantially equivalent to pre-amendment devices.

To further control the entry of new devices and provide continued monitoring postmarketing, the *1990 Safe Medical Devices Act* (SMDA) was enacted into law.[26] SMDA strengthened the 1976 Medical Device

Amendments and expanded the reporting criteria for adverse events related to devices. SMDA required manufacturers and user facilities (such as hospitals and nursing homes) to report events in which a device may have caused or contributed to a death.

The impact of the *FDA Modernization Act of 1997* (FDAMA) on medical devices was to streamline the premarket notification process. It directed the FDA to focus postmarket surveillance on higher risk devices and allowed for the implementation of a reporting system for user facilities.

The purpose of the *Medical Device User Fee and Modernization Act (MDUFMA)* of 2002 was to improve the device application review process in order to keep up with the rapid growth and increasing complexity of device technology. MDUFMA also:

- allowed the FDA to charge user fees for premarket reviews, thereby providing funding to hire the necessary personnel to enhance and accelerate the review of premarket applications;
- allowed for the establishment of an office to coordinate the review of combination products;
- authorized third party inspections.

Device Safety and Effectiveness

Device Safety – 21 CFR 860.7(d)(1)
There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Device Effectiveness – 21 CFR 860.7(e)(1)
There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

What is a Medical Device?

A medical device is any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices range from simple tongue depressors to complex programmable pacemakers with microchip technology. Devices include *in vitro* diagnostic products, including laboratory equipment and reagents. Certain electronic radiation-emitting products with medical applications, such as ultrasound and x-ray machines, are considered devices.[27] The FDA defines a medical device as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory, which is:

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man; or
- intended to affect the structure or any function of the body of man, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man, and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."[28]

Medical Device Classification

Devices have been divided into categories based on the level of risk and grouped according to the medical area of use. Devices are also categorized into significant and nonsignificant risk classes with associated regulatory requirements based on the risk assessment.

Regulatory Classes of Devices

Products that have met the definition of a medical device are assigned to a regulatory class based on the level of risk to users/subjects, and therefore, the level of control and FDA oversight necessary to assure the safety and efficacy of the device as labeled. Each device is assigned to one of three regulatory classes, depending on the level of control needed.

Class I devices present minimal potential for harm to the user and are subject to *General Controls*, the baseline requirements that apply to all classes of medical devices. Unless specifically exempted in the regulations, general controls require medical devices to be properly labeled and packaged, be cleared for marketing by the FDA (*premarket notification* [510(k)], meet their labeling claims, and be designed and manufactured under Good Manufacturing Practices (21 CFR 820). Manufacturers, distributors, repackagers, and relabelers of Class I devices must comply with the requirements for company registration and must submit *Form FDA 2892 Medical Device Listing* for devices to be marketed. The regulations exempt many Class I devices from premarket notification and/or good manufacturing practices regulations because the level of risk is low to the users. Examples of Class I devices include elastic bandages, examination gloves, and crutches.

Class II devices have been determined to require more than General Controls to assure safety and effectiveness and are subject to additional "Special Controls." *Special Controls* may include special labeling requirements, mandatory performance standards, patient registries, and postmarket surveillance. Many Class II devices require *premarket notification*, although a few are exempt from this requirement; examples of devices exempt from premarket notification include infusion pumps and surgical drapes. A small number of Class II devices require *premarket approval* with clinical trials to provide supporting data.

Class III devices are those determined to require additional regulatory oversight to assure safety and effectiveness beyond that established by General and Special Controls. Since Class III devices are usually those that support or sustain life, are of substantial importance in preventing health impairment, or which present a

Figure 2.2 Device Classes

Regulatory Class of Device	Regulatory Controls	Examples
Class I – Common, low-riskdevices	General Controls Most are exempt from premarket submission	• suction snake bite kit • non-sterile examination gloves • band-aids
Class II – More complex devices with moderate risk	Special Controls Premarket Notification [510(k)]	• powered wheelchair • acupuncture needles • surgical drapes
Class III – Most complex devices; highest risk Includes life sustaining and life supporting devices, devices of substantial importance in preventing health impairment, and devices that present a potentially unreasonable risk of illness or injury	Premarket Approval	• silicone breast implants • pacemakers • respiratory assist devices • heart assist devices

potential, unreasonable risk of illness or injury, most are subject to *premarket approval.*

Classification Panels

The FDA has established classifications for more than 1700 types of devices and grouped them into 16 medical specialties, or "panels," such as cardiovascular, dental, neurology, and radiology. These panels can be found in 21 CFR Parts 862 through 892.

Each classification panel provides a list of the generic names and an associated 7-digit number for all the devices included in the specialty. Devices are listed with an identification or description of the device, the regulatory class of device (I, II, or III) with or without exemptions or special controls, and the applicable marketing requirements for the device.

Device Risk Assessment

Based on the assessment of risk to users, devices are either categorized as *significant risk devices* and subject to clinical investigation under full Investigational Device Exemption (IDE) regulations, or categorized as *nonsignificant risk devices* and subject to abbreviated IDE regulations. A third category of device studies comprises those that are *exempt* from IDE regulations. The initial assessment of risk is made by the sponsor (usually the device manufacturer) and should be based on the proposed use of the device in the investigation.

Figure 2.3 Medical Specialty Panels for Device Classification

21 CRF §	Medical Specialty Panel
868	Anesthesiology
870	Cardiovascular
862	Clinical Chemistry and Clinical Toxicology
872	Dental
874	Ear, Nose, and Throat
876	Gastroenterology and Urology
878	General and Plastic Surgery
880	General Hospital and Personal Use
864	Hematology and Pathology
866	Immunology and Microbiology
882	Neurology
884	Obstetrical and Gynecological
886	Ophthalmic
888	Orthopedic
890	Physical Medicine
892	Radiology

Significant Risk Device

A *significant risk (SR) device* is one that presents a potential for serious risk to the health, safety, or welfare of a subject, and meets one of the criteria found in 21 CFR 812.3(m), such as an implant or a device that is life-supporting or life-sustaining, and devices that are substantially important in diagnosing, curing, mitigating or treating disease, in preventing impairment to human health. Examples include sutures, cardiac pacemakers, hydrocephalus shunts, and orthopedic implants.[29] Studies of SR devices must first have FDA approval obtained by submitting an IDE application; IRB approval must also be obtained before beginning clinical studies of the SR device.

Nonsignificant Risk Device

A *nonsignificant risk (NSR) device* is one that does not pose a significant risk to subjects and does not meet the above definition for significant risk. The NSR category was created to avoid delay and expense in situations where the anticipated risks did not justify FDA involvement. Nonsignificant risk device studies have fewer regulatory controls than significant risk studies and are regulated by

abbreviated requirements in 21 CFR 812.2(b), but must comply with the same IRB, informed consent, and financial disclosure regulations. They differ from significant risk studies in the approval process (sponsors are not required to submit an IDE application to the FDA), record keeping, and reporting requirements.

When a sponsor considers a study to be NSR, the sponsor provides the reviewing IRB with an explanation of its rationale and seeks IRB approval for an NSR study of the device. The IRB may ask the sponsor for additional information and may agree or disagree with the sponsor's assessment. If the IRB agrees with the NSR assessment and approves the study, no FDA submission or review is necessary before human studies begin. If the IRB disagrees with the NSR assessment, the sponsor must notify the FDA that a significant risk assessment has been made, and must submit an IDE application before starting clinical trials.

There is no requirement to report the start of an NSR study to the FDA; however, the requirements for IRB review, informed consent of all subjects, adverse event reporting, and labeling do apply. Therefore, when an NSR study is being conducted, the role of the IRB is very important because it is serving as the FDA's surrogate. Although an NSR study may begin immediately after IRB approval and without notifying the FDA, sponsors may want to voluntarily seek advice from or inform the FDA about the study, since the FDA has the authority to later disagree with the NSR assessment.

To assist sponsors and IRBs in the determination of risk, the FDA provides examples of devices in each category. The chart below includes examples of nonsignificant risk and significant risk devices. For a comprehensive list, refer to the Information Sheets about

Figure 2.4 Examples of Significant Risk and Nonsignificant Risk Devices

Device	NSR	SR	IDE Application	FDA Approval Before Start of Study	IRB Approval Before Start of Study	Informed Consent
Daily wear contact lens	X				X	X
Extended wear contact lens		X	X	X	X	X
Conventional laparoscope	X				X	X
Catheters introduced into fallopian tubes		X	X	X	X	X
Externally worn monitors for insulin	X				X	X
Implantable defibrillator		X	X	X	X	X

medical devices (http://www.fda.gov/oc/ohrt/irbs/devrisk.pdf) and the Center for Devices and Radiologic Health (CDRH) Web site (www.fda.gov/cdrh).

Requirements for Marketing New Devices

Similar to investigational drugs and biologics, some devices require FDA authorization in order to conduct clinical trials before the FDA provides marketing approval. Unlike drugs that fall into only one regulatory category, a device is subject to different regulations, depending on which of the three categories (Premarket Notification, Premarket Approval, IDE-Exempt) applies.

Substantially Equivalent Devices

When determining the necessary regulatory requirements to market a device, the sponsor should refer to the devices listed in the Specialty Panels in 21 CFR 862 to 892. A device may be exempted from Premarket Notification if it is determined to be "substantially equivalent" to a device that was marketed before the Medical Device Amendments of 1976 or if a Premarket Notification was submitted by another person or sponsor. If the new device is deemed substantially equivalent to a pre-amendment (also called predicate) device, it may be marketed immediately and is regulated in the same regulatory class as the pre-amendment device to which it is equivalent. The device sponsor or manufacturer cannot market the device in the United States until the FDA declares the device to be substantially equivalent. Many devices are cleared for commercial distribution in the United States by this process.

Substantial equivalence means that when compared to the pre-amendment device, the new device:

- has the same intended use and the same technological characteristics, or
- has different technological characteristics that do not raise new safety and effectiveness questions, assuming the sponsor demonstrates that the new device is as safe and effective as the predicate device.

Devices that Require Premarket Notification [510(k)]

When the FDA determines that a device is substantially equivalent to a pre-amendment device, Class I, Class II, and some Class III devices can be marketed using the *premarket notification [510(k)]* process. This applies to devices introduced to the U.S. market *after* the 28 May 1976 amendment, that are substantially equivalent to a device introduced to the U.S. market *before* the 28 May 1976 amendment.[30] When Premarket Notification is required, it must be submitted at least 90 days before introduction into interstate commerce for commercial distribution.[31]

Some of the items required in a Premarket Notification (PMN) are:

1 device name (trade and proprietary names);

2 registration number of the person or manufacturer submitting the PMN;

3 device class and specialty panel;

4 proposed labeling and advertisements.

For a complete listing of the information required in a Premarket Notification refer to 21 CFR 807.87.

Devices that Require an IDE Application

The higher complexity and greater risks associated with SR devices requires the manufacturer or sponsor to submit an IDE application to the FDA to provide supporting clinical data for a Premarket Approval application. Similar to the IND application required for studies of investigational drugs and biologics, this exemption allows manufacturers to ship investigational medical devices for use in clinical trials to collect safety and effectiveness data. An IDE is also required to conduct clinical studies when a manufacturer proposes modifications or new uses of a legally marketed device. The sponsor or manufacturer must obtain an approved IDE before beginning a clinical study.

The sponsor must submit a completed IDE application to the FDA and the investigational plan to the IRB of each institution where the study will be conducted. The FDA does not provide IDE forms, such as the Form FDA 1571 required for sponsors of drug studies, or the Form FDA 1572 for investigators, but the IDE application must include all elements found in 21 CFR 812.20. Upon receipt of the application, the FDA provides written notice of receipt and assigns an IDE number to the device application. An IDE application is considered approved 30 days after FDA receipt, unless the FDA informs the sponsor otherwise.

IDE regulations apply to most but not all clinical studies performed in the United States to collect safety and effectiveness data about an investigational medical device. IDE requirements can be found in 21 CFR 812. All clinical investigations of medical devices must comply with the same informed consent and IRB regulations that govern investigations of drugs and biologics in 21 CFR 50 and §56, as well as financial disclosure regulations in 21 CFR 54.

IDE-Exempt Studies (or IDE-Exempted Investigations)

Certain trials of devices may be exempt from the full IDE requirements (for SR device studies) or abbreviated IDE requirements (for NSR device studies). Human device studies that are exempt include the following:

1 a legally marketed device when used according to its labeling;

2 a diagnostic device that is compliant with the labeling requirements and is:
   (a) noninvasive;
   (b) does not require an invasive sampling procedure that presents a significant risk;
   (c) does not by design or intention introduce energy in a subject;
   (d) is not used as a diagnostic procedure without confirmation by an established diagnostic procedure;
3 consumer preference testing.

Full criteria for exempted device investigations can be found in 21 CFR 812.2. The sponsor should determine whether the device study exempted from IDE requirements is also exempted from the requirements for IRB review and approval and written informed consent.

Devices that Require Premarket Approval

After completion of trials that demonstrate device efficacy and safety, most Class III devices require *Premarket Approval (PMA)* which is similar to the NDA required before marketing new drugs or the Biologics License Application to market new biologics. PMA is the review process used by the FDA to ensure the device's safety and effectiveness; PMA is required of devices:

1 regulated as new drugs before 28 May 1976;
2 found not substantially equivalent to devices marketed before 28 May 1976; or
3 that are Class III pre-amendment devices which require a Premarket Approval Application.

Device clinical trials conducted to support a PMA require:

1 An IDE application approved by an IRB (if the device is a significant risk device, the IDE must also be approved by the FDA);
2 informed consent from all subjects;
3 labeling that identifies the device for investigational use only;
4 monitoring of the study;
5 applicable records and reports.

Approval of a PMA submission is given when the FDA determines there is evidence that the device is safe and effective for its intended use. PMA regulations can be found in 21 CFR 814.

Steps to Approval and Marketing of Devices

STEP 1: Confirm that the device meets the medical device definition.

STEP 2: Determine the classification (I, II, or III), risk assessment (SR or NSR), and the appropriate marketing process (either Premarket Notification [510(k)] or Premarket Approval, unless exempt from both).

STEP 3: Develop the data and/or information needed to submit the marketing application to obtain FDA clearance for marketing. Some [510(k)] submissions and most PMA applications require clinical trials conducted under IDE regulations.

Humanitarian Use Devices

Examples of Humanitarian Use Devices include the Reclaim™ Deep Brain Stimulation device for the treatment of chronic, severe, treatment-resistant Obsessive Compulsive Disorder (OCD); Epicel®, a cultured epidermal autograft indicated for use in patients who have deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%; and Enterprise Vascular Reconstruction Device and Delivery System, a vascular reconstruction device and delivery system for use with embolic coils for the treatment of wide-neck, intracranial, saccular, or fusiform aneurysms.[33]

Humanitarian Use Devices

Unlike drugs and biologics, medical devices are not eligible to be classified as "orphan" products. To address this problem, the Safe Medical Device Act of 1990 included a provision for a humanitarian device exemption to encourage the discovery and use of devices intended to treat or diagnose a rare disease or condition (defined as one that affects fewer than 4000 individuals in the U.S. per year, in contrast to fewer than 200,000 individuals required for orphan drug designation). The regulations provide for the submission of a Humanitarian Device Exemption (HDE) application, which is similar in form and content to a PMA application, but is exempt from the PMA's requirements for effectiveness.[32] This allows a medical device to be approved with the evidence that the probable health benefit of the device is greater than the risk of use.

Early or Expanded Access to Unapproved Medical Devices

Normally unapproved medical devices may only be used in humans in the context of clinical testing that complies with IDE requirements. However, circumstances may arise in which a physician wants to use an unapproved device to save a patient's life or to relieve suffering from a serious disease for which there is no alternative treatment. The FDA provides the following mechanisms for allowing early or expanded access to an unapproved device.

Emergency Use

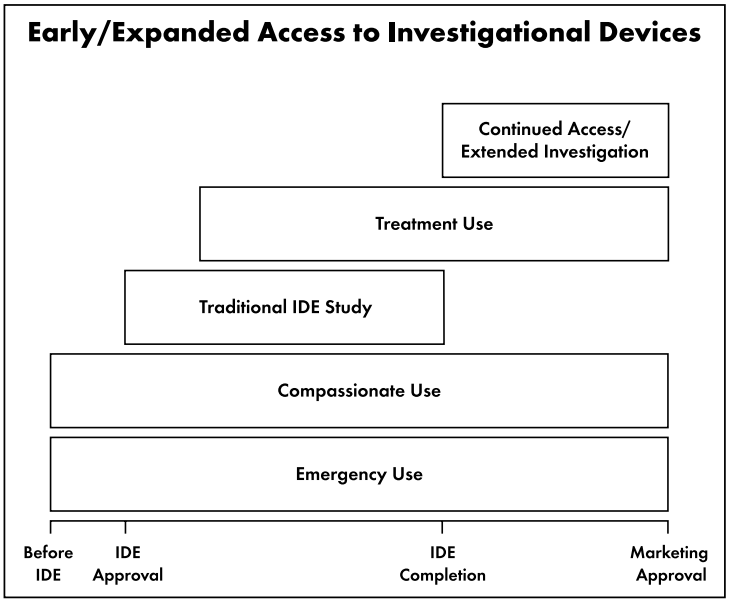
Emergency situations may occur where there is a need to use an unapproved device in a manner that differs from the use prescribed in the clinical study or by a physician who is not participating in the study. The criteria for emergency use are that: 1) the patient is faced with a life-threatening or serious disease/condition; 2) there is no alternative treatment available; and 3) there is not enough time to obtain FDA approval. Emergency use can occur any time before, during, or after the clinical study of the device.

Compassionate Use

Compassionate use of an unapproved device may occur when patients do not meet the eligibility criteria for study entry but the physician believes the device may provide benefit to the patient. Approval for compassionate use is typically granted for individuals, but may also be given for a small group of patients when the disease

or condition is serious and there is no alternative treatment available. Compassionate use may occur anytime during a clinical trial; FDA approval is required before compassionate use of the device can occur.

Figure 2.5 Early and Expanded Access to Devices



Treatment Use

The treatment use provision of the IDE provides desperately ill patients with access to promising new devices before marketing approval has been granted. A treatment IDE application must be submitted to the FDA, after which the FDA has 30 days to respond with notice of approval or disapproval. Treatment use of the device can occur during clinical studies of the device.

Continued Access/Extended Investigation

Continued enrollment of subjects after the completion of a clinical trial provides access to the medical device during the time when the marketing application is being prepared for submission to the FDA. Continued Access Use may be granted when there is a public health need for the device or when preliminary evidence shows that the device is likely to be effective without significant safety concerns. The sponsor should submit the request for continued access/extended investigation via an IDE supplement.[34]

FDA Device Review

The FDA is responsible for regulating businesses that manufacture, repackage, relabel, and/or import medical devices sold in the United States.[35]

CDRH

Review of medical devices is primarily performed by the *Center for Devices and Radiologic Health* (CDRH) within the FDA. The CDRH is responsible for developing and implementing programs to protect public health in the areas of medical devices and radiologic health. CDRH also regulates radiation-emitting electronic products (medical and nonmedical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens, and color televisions. CDRH protects the public health by providing reasonable assurance of the safety and effectiveness of medical devices and by eliminating unnecessary human exposure to radiation emitted by electronic products.

FDA Advisory Committees

Just as CDER and CBER have established external advisory committees for drugs and biologics, the CDRH has established advisory committees to provide independent, professional expertise and technical assistance regarding the development, safety and effectiveness, and regulation of medical devices and electronic products that produce radiation. The advisory committees to CDRH offer recommendations, but final decisions are made by FDA.

Combination Products

A new category of medical products is that of *combination products*, which have both drug and device actions. A combination product is defined in the regulations as:

1 A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity.

2 Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products.

3 A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to

achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.

4 Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.[36]

Examples of combination products include coated artificial joints, drug-eluting stents, and nonreusable syringe needle applicators with insulin for one-time injection. FDA review groups for drugs (CDER), biologics (CBER), and devices (CDRH) work together to review combination products. Evaluations of the product must consider both the drug actions and device components; however, depending on the primary action of the product, one of the review groups will be assigned as the lead center with primary reviewing responsibilities.

In the following chart there are two examples of combination products – drug-eluting coronary artery stents and drug-eluting disks for cancer therapy. Based on the primary action of each product, an assignment was made to regulate the stent as a device and the disk as a drug.

Combination Product	Drug-Eluting Stent	Drug-Eluting Disk
Primary mode of action	Stent opens artery	Cancer chemotherapy for brain tumor
Secondary mode of action	Drug prevents inflammation and restenosis	Local drug delivery by device
Regulated as	Device (PMA)	Drug (NDA)[37]

Postmarketing Surveillance of Drugs, Biologics, and Devices

Active postmarketing surveillance of adverse effects for all marketed products is essential to identify side effects and problems that did

not appear during the clinical testing phases. While premarketing clinical trials may involve several hundred to several thousand patients, some adverse events and problems can only be detected after a product has been used by many thousands of people. The FDA has established a system of surveillance and risk assessment to monitor events such as adverse reactions, poisonings, and device malfunction. This postmarketing information may be used to update labeling and package inserts, and even to re-evaluate the approval or marketing decision when indicated.

Once a product has FDA approval for marketing, the sponsor must continue to report information about the approved product to the FDA for the lifetime of the product. Health care providers report new findings and/or adverse events about marketed products: 1) in the context of a phase 4 postmarketing study; or 2) by direct reporting to the product manufacturer or the FDA based on the observation of subjects receiving the treatment.

Postmarketing Drug Recall

Vioxx was a COX-2 selective nonsteroidal anti-inflammatory drug approved in 1999 for the treatment of arthritis. In 2004, the drug manufacturer recalled Vioxx based on new information from a clinical study (APPROVe) which showed an increased risk of cardiovascular events such as heart attack and stroke beginning after 18 months of treatment. APPROVe (Adenomatous Polyp Prevention on Vioxx) was being conducted to determine the effect of Vioxx on the recurrence of neoplastic polyps of the large bowel in patients with a history of colorectal cancer; the study was stopped early because of the increased risk of cardiovascular events.[38]

Phase 4 Postmarketing Drug and Biologics Studies

Once a drug treatment has been approved and marketed, additional information may be collected in phase 4 trials. These studies are generally conducted to monitor long-term safety and effectiveness, and to learn how well the product works when used in "real-life" conditions. Phase 4 studies may also be conducted to test different dosages or administration schedules, to evaluate delayed versus sustained-release formulations, or to study patient subgroups, such as minorities, women, or children. The FDA sometimes requires the sponsor to conduct long-term safety trials to obtain additional safety data, for example, on new types of drugs or biologics, or when a drug has been "fast-tracked." Phase 4 studies can further establish the safety and efficacy of the product and thereby gain greater market acceptability for the product. Phase 4 studies are also conducted to familiarize practicing physicians with the new drug and thereby increase its usage.

Phase 4 Postmarketing Device Studies

Because devices are often approved on data that are collected over relatively short periods of use, postmarketing data collection is critical to understanding the long-term safety and effectiveness of a device. The collection of outcome and adverse event data pertaining to a device after it is marketed may be done in a phase 4 study.

Postmarketing data collection is sometimes required by the FDA, but at other times is done at the discretion of the sponsor. The *Safe Medical Devices Act* of 1990 requires postmarketing surveillance studies on all devices marketed after January 1, 1991, that:

(1) are permanent implants, the failure of which may cause serious, adverse health consequences or death;

(2) are life-supporting or life-sustaining; or

(3) may pose a serious risk to human health.[39]

Postmarketing surveillance is intended primarily to study the performance of a device as used in its target population and to serve as a warning system for detecting potential problems.

Upon PMN or PMA acceptance, manufacturers will receive notice from the FDA indicating whether the device is subject to postmarketing surveillance. When postmarketing surveillance is required, the sponsor/manufacturer must submit a protocol to the FDA within 30 days of introducing the device into interstate commerce.

Direct Reporting Based on Observations

Direct reporting by health care providers is just as important as postmarketing studies and provides essential information regarding the safety of medical products.

MedWatch

While the FDA is responsible for assuring the safety and effectiveness of all regulated marketed drugs, biologics, and devices, the health care professionals who monitor patients and report adverse events and product problems are integral to this process. MedWatch, the FDA's safety information and adverse event reporting program, was established to educate health professionals and consumers about the critical importance of monitoring and reporting events and problems, as well as to collect and rapidly communicate new safety information to the public and medical community. The use of MedWatch enhances the effectiveness of postmarketing surveillance of medical products, including prescription and over-the-counter drugs, biologics, medical and radiation-emitting devices, and special nutritional products (e.g., medical foods, dietary supplements, and infant formulas) used in clinical practice; further, it helps to rapidly identify significant product-associated health hazards.[40]

Historically, serious adverse events and product problems have been significantly under-reported. This is most likely due to the challenges of determining whether an event is expected or unexpected in the progression of a disease, as well as whether the medical product caused or was coincidental to the event or problem. To improve reporting, MedWatch has provided clarification of events

and problems that should be reported and has simplified reporting for health professionals.

Manufacturers are obligated by law to report to the FDA any device malfunctions, as well as any deaths or serious injuries that a product-related adverse event may have caused or contributed to. User facilities (such as hospitals and nursing homes) must report deaths and serious injuries related to a device that occur within a user facility; reports should be made to the manufacturer, or if the manufacturer is unknown, to the FDA.

While the reporting of adverse events and problems with drugs and biologics is strictly voluntary on the part of health care professionals, reporting of all medical products by health care professionals is vital to the successful and comprehensive postmarketing surveillance of medical products. Reporting can contribute to modifications in the use or design of a product and improve the safety profile of a drug or device, ultimately leading to improved patient safety.

Voluntary Reporting

Form FDA 3500 is the form designed for ***voluntary*** reporting of adverse events and product problems noted spontaneously in the course of clinical care by health care professionals and consumers. When physicians and other health care providers become aware of serious adverse events and product problems in patients outside the setting of a study, the events should be reported either to the product manufacturer or to the FDA using the MedWatch form.

The MedWatch program asks health care professionals and consumers to report:

- Any serious adverse event that might be associated with a drug, biologic, medical device, or dietary supplement; "serious" refers to fatalities, hospitalizations, and medically significant events, especially those not listed in product labeling or package insert.
- Therapeutic failures – cases where the drug or device failed to work as it should.
- Cases of usage errors, including situations where the error may have been due to poor communication, or to ambiguities in product names, directions for use, or packaging.
- Product quality issues, such as suspected counterfeit products, defective components, potential contamination, device malfunctions, and poor packaging.[41]

Form FDA 3500 can be used to report experiences with drugs, biologics, medical devices, special nutritional products, and other

Vaccine Reporting

Serious adverse events related to vaccines should not be reported on the Form FDA 3500, but through the Vaccine Adverse Event Reporting System (VAERS) found at http://vaers.hhs.gov/.

FDA-regulated products. Form FDA 3500 may be submitted online (www.fda.gov/medwatch/report.htm), or by mail, telephone, or fax, although if the product reaction is dangerous or life-threatening, the report should be made by telephone.

Health care providers who may be concerned about confidentiality of information when submitting postmarketing problems should be aware that the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule is not intended to discourage or prevent adverse event reporting. It does, however, require those submitting the adverse event report to make a reasonable effort to submit the minimum amount of protected health information necessary to complete the report.[42]

> The HIPAA Privacy Rule recognizes the legitimate need for public health authorities and others responsible for ensuring public health and safety to have access to protected health information to carry out their public health mission. The Rule also recognizes that public health reports made by covered entities are an important means of identifying threats to the health and safety of the public at large, as well as individuals. Accordingly, the Rule permits covered entities to disclose protected health information without authorization for specified public health purposes.[43]

Mandatory Reporting

FDA Form 3500A is the form designed for the ***mandatory*** reporting of adverse events and product problems by medical product manufacturers, packers, distributors, and user facilities. Manufacturers and user facilities (hospitals and nursing home) are required to report deaths and serious injuries that have or may have been caused by (or contributed to) by the use of a medical product. Doctors' offices are not considered user facilities and should complete Form FDA 3500 rather than Form FDA 3500A.

Currently Form FDA 3500A cannot be submitted online; paper copies must be completed and submitted to CDRH at the FDA. Regulations regarding the postmarketing reporting of adverse drug experiences can be found in 21 CFR 314.80, biologics in 21 CFR 600.80, and devices in 21 CFR 803.

MedWatch Forms

FDA Form 3500 – **voluntary** reporting by health care providers and consumers

FDA Form 3500A – **mandatory** reporting by manufacturers and user facilities

Figure 2.6 MedWatch Form 3500

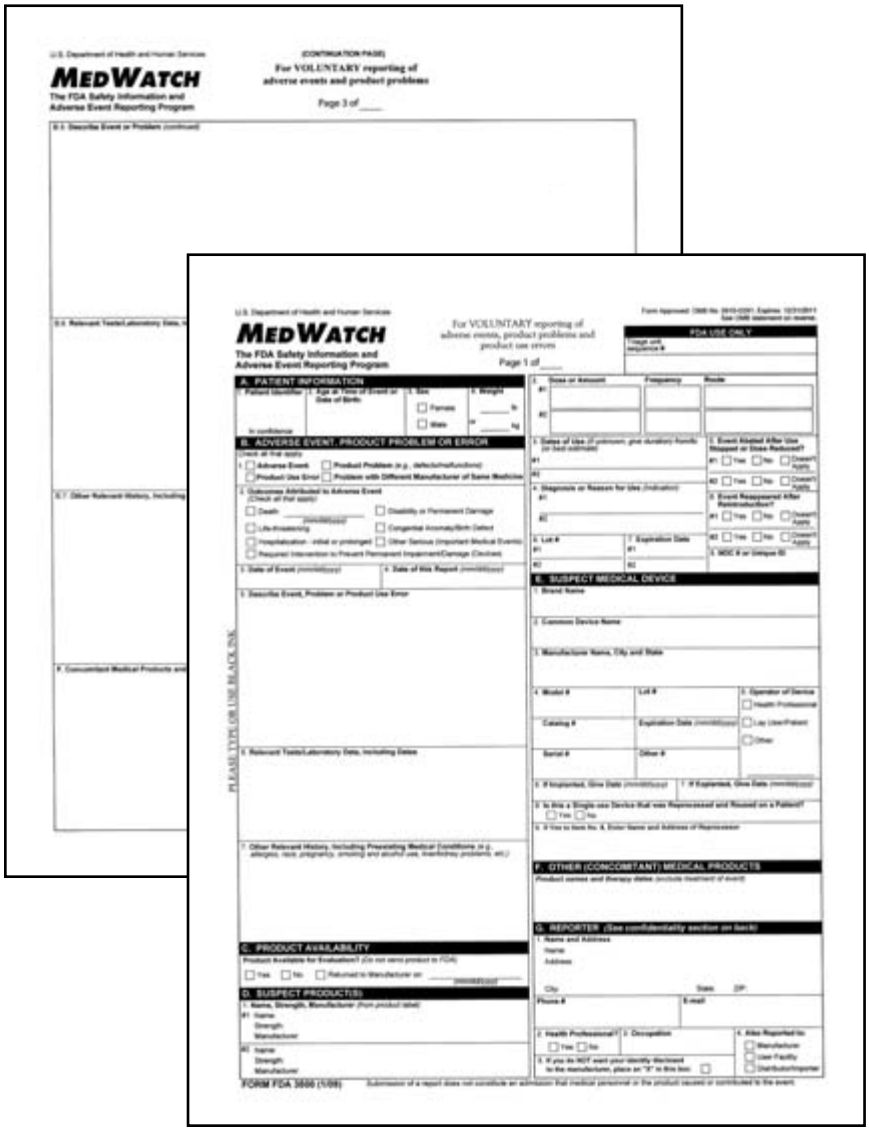
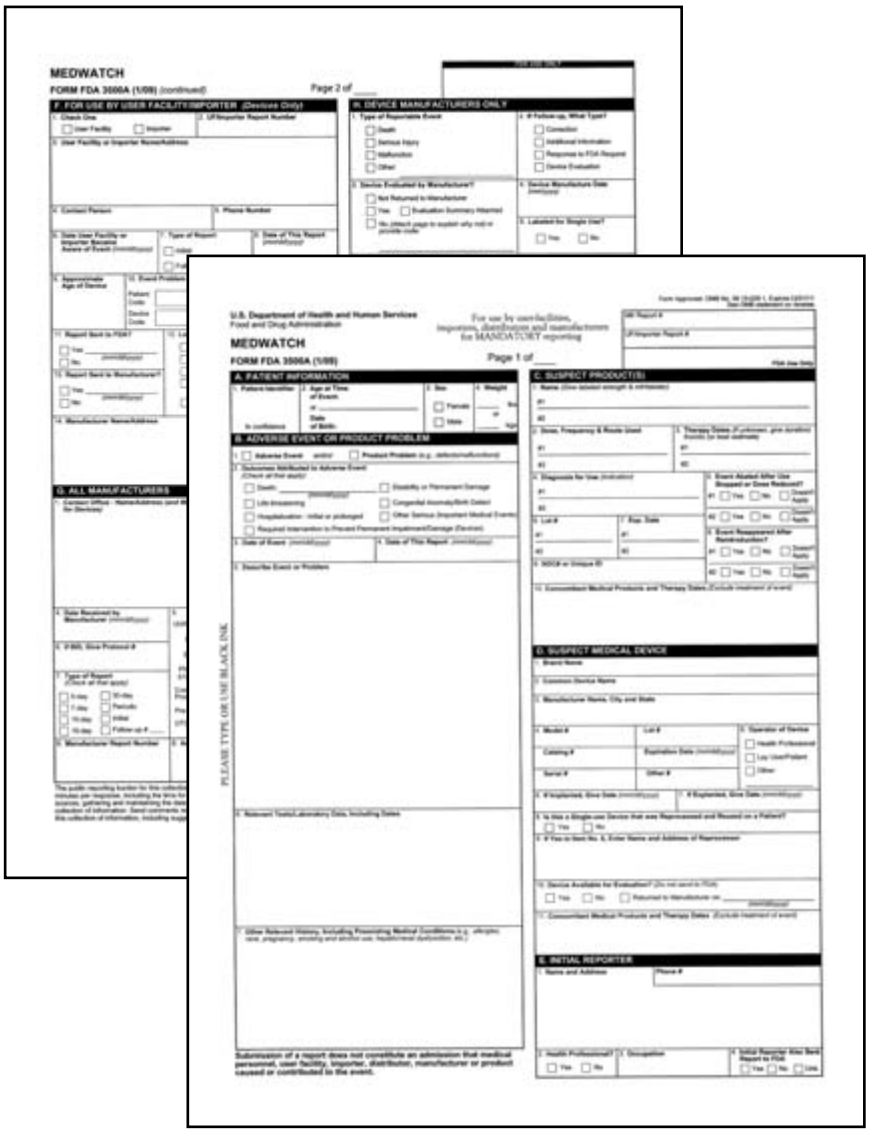


Figure 2.7 MedWatch Form 3500A



MEDWATCH
FORM FDA 3500A (1/09) (continued)
Page 2 of ____
F. FOR USE BY USER FACILITY/IMPORTER (Device Only)
G. DEVICE MANUFACTURERS ONLY
H. ALL MANUFACTURERS

U.S. Department of Health and Human Services
Food and Drug Administration
MEDWATCH
FORM FDA 3500A (1/09)
For use by user facilities, importers, distributors and manufacturers for MANDATORY reporting
Page 1 of ____
A. PATIENT INFORMATION
B. ADVERSE EVENT OR PRODUCT PROBLEM
C. SUSPECT PRODUCT(S)
D. SUSPECT MEDICAL DEVICE
E. INITIAL REPORTER
PLEASE TYPE OR USE BLACK INK
Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

Figure 2.8 Drugs and Biologics

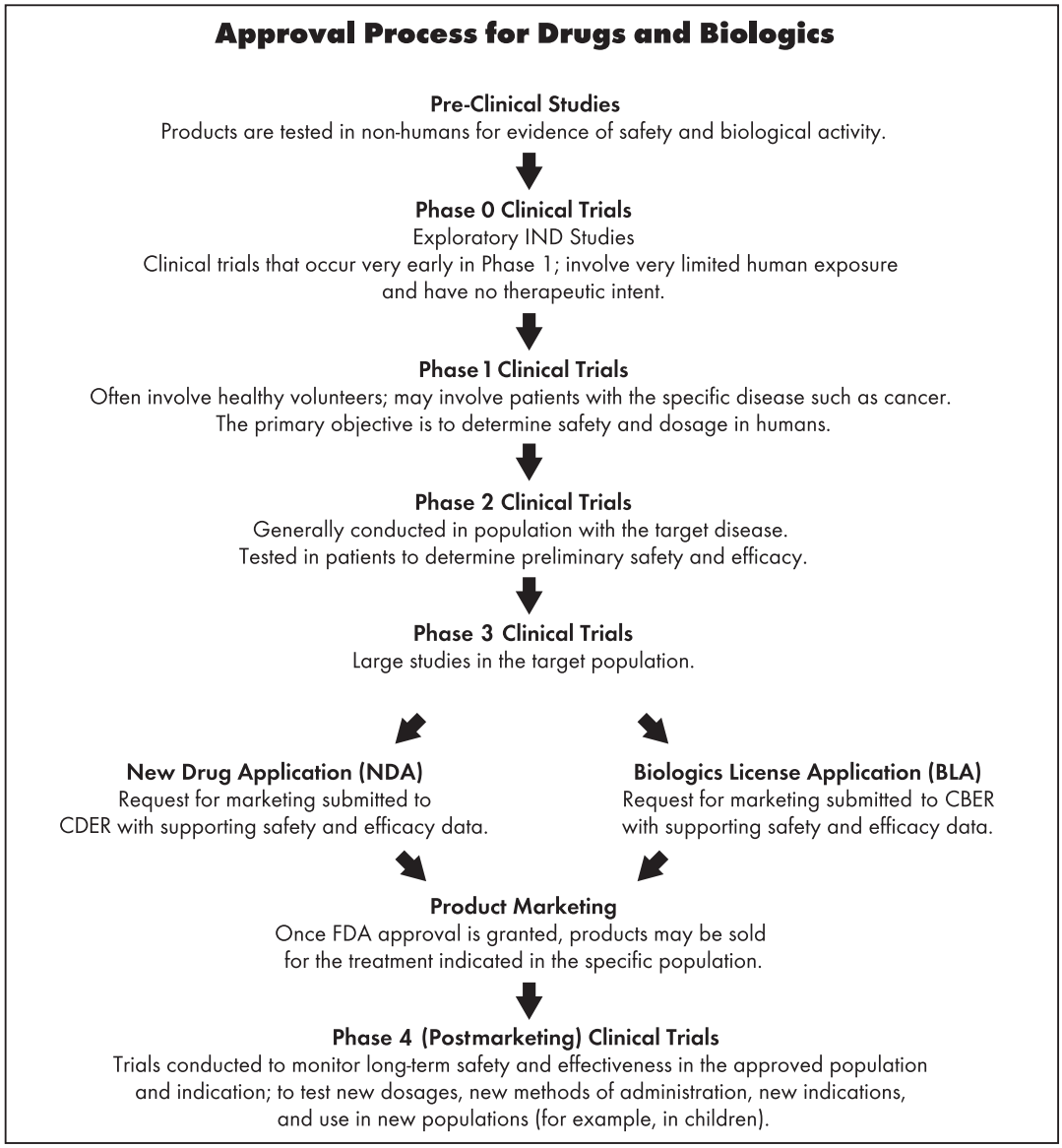
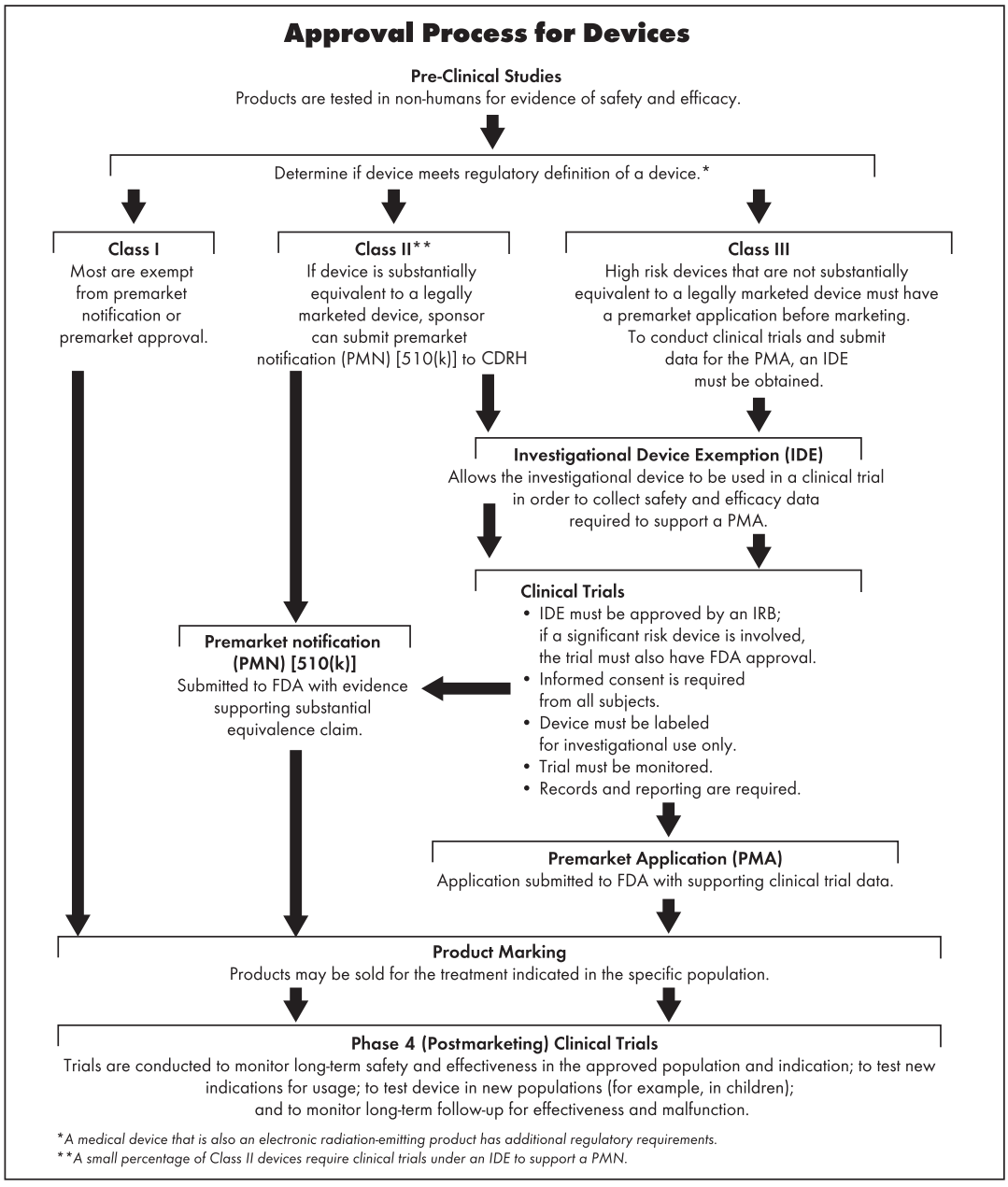


Figure 2.9 Devices



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3 21 CFR 312.42 Clinical holds
4 21 CFR 312.21 Phases of an investigation
5 http://www.cancer.gov/newscenter/pressreleases/PhaseZeroNExTQandA
6 http://www.fda.gov/cder/guidance/6384dft.htm
7 http://www.cancer.gov/newscenter/pressreleases/PhaseZeroNExTQandA
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11 http://www.fda.gov/CBER/faq.htm#1
12 http://www.fda.gov/CBER
13 http://stemcells.nih.gov/info/basics/basics1.asp
14 http://www.fda.gov/CbER/gdlns/fsttrk.pdf: Guidance for Industry: Fast Track for Drug Development Programs; January 2006
15 http://www.fda.gov/cder/rdmt/NDAapps93-06.htm
16 http://www.fda.gov/Cder/rdmt/default.htm
17 21 CFR 312.34(a) Treatment use of an investigational new drug
18 FDA Information Sheet: Treatment Use of Investigational Drugs, October 1, 1995
19 http://irb.mc.duke.edu/InvestigationalProducts.htm
20 FDA Information Sheet: Treatment Use of Investigational Drugs, October 1, 1995
21 21 CFR 312.36 Emergency use of an investigational new drug
22 http://www.fda.gov/consumer/updates/oda020808.html
23 http://www.fda.gov/fdac/special/newdrug/orphan.html: Orphan Products: New Hope for People with Rare Disorders
24 http://www.fda.gov/consumer/updates/oda020808.html
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27 http://www.fda.gov/cdrh/devadvice/312.html: Is the Product a Medical Device?
28 http://www.fda.gov/cdrh/devadvice/312.html#link_2
29 http://www.fda.gov/cdrh/devadvice/ide/approval.shtml
30 http://www.fda.gov/cdrh/devadvice/3132.html: Device Classes
31 21 CFR 807.81(a)
32 www.fda.gov/cdrh/newdevice.html
33 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm
34 http://www.fda.gov/cdrh/devadvice/ide/early.shtml#continuedaccess
35 http://www.fda.gov/cdrh/devadvice/overview.html
36 21 CFR 3.2(e)
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39 U.S. Congress, Safe Medical Device Amendments to the Food, Drug & Cosmetic Act, Section 522(a)(1)(1990)
40 http://www.fda.gov/medwatch/what.htm
41 MedWatch: Reporting Adverse Events: March 2008. www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm
42 http://www.fda.gov/medwatch/hipaa.htm
43 From OCR Guidance Explaining Significant Aspects of the Privacy Rule – Disclosures for Public Health Activities, p. 28. See also 45 CFR 164.512 (b)(1)(i) and (iii)

3 Good Clinical Practice and the Regulations

In this Chapter

- Good Clinical Practice
- The Code of Federal Regulations
- HIPAA and the Privacy Rule
- ICH Guidelines
- Responsibilities of Investigators, IRBs, and Sponsors

The regulations quoted in this chapter are current as of the date of this printing. Refer directly to the U.S. Code of Federal Regulations, the Federal Register, FDA guidance documents, and the ICH Web site to obtain the most current information regarding the regulations and guidelines. A list of pertinent U.S. regulations and ICH E6 guidelines is provided in Appendix E.

"Sometimes it is not enough to do our best; we must do what is required."
Sir Winston Churchill (1874–1965), British Prime Minister during World War II

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

Most clinical research done in the United States comes under federal regulatory authority either because it involves the study of drugs, biologics, and devices regulated by the Food and Drug Administration (FDA) or because it receives funding from federal agencies such as the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC). These agencies are all part of the U.S. Department of Health and Human Services (DHHS), and their regulations, supported by the standards provided in Good Clinical Practice, combine to provide an ethical regulatory framework to conduct clinical trials of new medical products in the United States.

Good Clinical Practice

Good Clinical Practice (GCP) is a broad term that refers to the generally recognized standards for conducting clinical research studies. These standards apply to all aspects of clinical trials, from protocol design, monitoring, and auditing, to recording, analysis, and reporting of research data. The overriding aim of GCP is to protect public health and the rights, welfare, and confidentiality of research participants. Furthermore, the GCP process has been put in place to ensure that all data and reported results are credible and accurate. While GCP places value on the results of the research studies, it also recognizes the importance of the processes used to conduct the studies.

GCP includes:

1. Regulations that are enforceable by law.
2. Guidelines that are part of the generally accepted practice although not enforceable by law.
3. Local laws that affect a specific region, city, or state.

GCP

Good Clinical Practice – A general term referring to standards for how clinical trials should be conducted including:

- Regulations
- Guidelines
- Local laws

Regulations

Federal regulations authorizing the U.S. government to oversee the safety of drugs date back to 1906, when the *Pure Food and Drugs Act* was passed by Congress. Subsequent regulations pertaining to clinical research were developed in response to a general consensus that research in humans should be ethical and based on the principles set forth in documents such as the Declaration of Helsinki (last amended in 2008) (see Appendix A) and the 1979 *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (known as The Belmont Report) (see Appendix A).

Code of Federal Regulations

The regulations for departments and agencies within the United States government are published in the Code of Federal Regulations (CFR). These regulations are issued by various executive departments and agencies and are divided into fifty "titles," each assigned to a specific agency and covering subjects ranging from agriculture and banking, to clinical research, internal revenue, and wildlife. CFR titles have been divided into chapters under the name of the issuing agency and then further separated into "parts" and "subparts."

Regulations that govern the conduct of clinical trials are published in Title 21 and Title 45 of the CFR. Title 21 regulations apply to clinical investigations of *products regulated by the FDA*, while Title 45 applies to clinical investigations based on *funding provided by the federal government*. The regulations identify the legal responsibilities of study sponsors, investigators, monitors, institutional review boards, contract research organizations, and regulatory authorities. The CFR also contains regulations for laboratories and manufacturers involved in clinical research. Each volume of the CFR is updated once each year; Title 21 is updated in April every year and Title 45 every October.

Title 21 of the Code of Federal Regulations

The CFR title containing the regulations that apply to clinical trials of investigational products regulated by the FDA is *Title 21*. The parts and subparts listed in the chart on this page are the regulations most relevant to clinical research conducted under the FDA.

Title 45 of the Code of Federal Regulations

Title 45, Part 46 provides regulations for trials supported wholly or in part by federal funding. As the federal government's primary

The **Code of Federal Regulations** is: 1) a system to codify (classify) the final rules/regulations published in the Federal Register, 2) arranged under fifty titles and further subdivided into chapters, parts, and subparts, and 3) enforceable by law.

Title 21: Food and Drugs

Chapter 1: Food and Drug Administration

Part 11:	Electronic Records; Electronic Signatures	
Part 50:	Protection of Human Subjects	
	Subpart B:	Informed Consent of Human Subjects
	Subpart D:	Additional Safeguards for Children in Clinical Investigations
Part 54:	Financial Disclosure by Clinical Investigators	
Part 56:	Institutional Review Boards	
Part 312:	Investigational New Drug Application (IND)	
	Subpart D:	Responsibilities of Sponsors and Investigators
Part 601:	Biologics License Application	
Part 812:	Investigational Device Exemption (IDE)	

Title 45: Public Welfare – Department of Health and Human Services

Part 46:	Protection of Human Subjects	
	Subpart A:	Basic Policy for Protection of Human Research Subjects (Common Rule)
	Subpart B:	Additional Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research
	Subpart C:	Additional Protections Involving Prisoners as Subjects
	Subpart D:	Additional Protections for Children Involved as Subjects in Research
Part 164:	Standards for Security and Privacy of Individually Identifiable Health Information (implementation of HIPAA)	

agency for advancing knowledge in the biomedical and behavioral sciences to understand and treat human disease, the NIH provides funds for clinical research conducted by investigators at outside institutions. Investigators who receive federal funding are required to follow the regulations in Title 45, Part 46, issued in 1991.

The *Federal Policy for the Protection of Human Subjects* is contained in 45 CFR 46 Subpart A. It is known as the **Common Rule** because it is the basic, or fundamental, policy for the protection of human research subjects. The primary elements of the Common Rule are requirements for: 1) assurance of compliance by research institutions, 2) obtaining and documenting informed consent, and 3) institutional review board (IRB) membership and activities. The Common Rule regulations have been agreed upon by 17 government agencies so that human subject research can be regulated consistently across the U.S. government. In addition to the Common Rule, 45 CFR 46 Subparts B, C, and D have been adopted to provide additional protection for vulnerable subjects.

Title 45 also contains the regulations for the *Privacy Rule* implementation of the *Health Insurance Portability and Accountability Act* known as HIPAA. These regulations found in 45 CFR Part 164 are applicable to the protection of health information collected during clinical trials by investigators and sponsors.

Differences Between Human Subject Protection Regulations in Title 21 and Title 45

The regulations in both 21 CFR 50 and 45 CFR 46 embody the ethical principles of The Belmont Report, which serve as a framework to ensure that serious efforts have been made to protect the rights and welfare of human subjects. Although the regulations in Title 21 are similar to those in Title 45, there are some differences due to the statutory scope and specific agency requirements. A comparison of the regulations can be found in *Comparison of FDA and DHHS Human Subject Protection Regulations*.[1]

Some of the primary regulatory differences between Title 21 (for products regulated by the FDA) and Title 45 (for federally funded trials) are:

- A written Federalwide Assurance is required from institutions receiving federal funding for clinical trials. The written assurance documents the institution's commitment to comply with human subject protection regulations, the regulations for IRB membership and procedures, and reporting responsibilities for unanticipated problems involving risks to subjects or others. FDA regulations in Title 21 do not have the same requirements for written assurances of compliance with the regulations.

- Title 45 Subparts B, C, and D provide additional protection for vulnerable populations, including pregnant women, human fetuses, neonates, prisoners, and children. Title 21 Part 50 Subpart D provides additional safeguards for children participating in clinical trials.
- The FDA has additional IRB requirements contained in 21 CFR Part 312 (Investigational New Drug Application) and Part 812 (Investigational Device Exemptions) as warranted by the type of product under investigation.
- Investigators who receive federal funding for clinical trials (and comply with 45 CFR 46) must indicate that all key personnel involved in the research have received training in the protection of human subjects.[2] There are only general references to information and training in 21 CFR 312.50 and 812.40, *General Responsibilities of Sponsors*, which state: "Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly . . ."
- Investigators who apply for federal funding for clinical research must submit, as part of the research application, a description of the data and safety monitoring plan for phase 1 and 2 trials, and a plan for a data safety monitoring board for phase 3 trials.[3]

The *NIH Revitalization Act*, signed into law in 1993, directed the NIH to establish guidelines to ensure the inclusion of women and minorities in clinical research. Amended in 2001, this act requires women and members of minority groups and their subpopulations to be included in all NIH-funded clinical research unless a clear and compelling rationale and justification establishes that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Protocols must describe the composition and rationale for the proposed study population in terms of sex/gender and racial/ethnic groups. Protocols must also provide a plan for proposed outreach programs to recruit women and minorities.[4]

Assurance of Compliance with Title 45 Regulations

DHHS human subject protection regulations and policies require that institutions engaged in non-exempt human subjects research supported by federal funding must submit a written assurance of compliance to the Office for Human Research Protections (OHRP). The written assurance, called a Federalwide Assurance (FWA), documents the institution's commitment to comply with the regulations for the protection of human subjects in 45 CFR 46

Vulnerable Subjects in Federally Funded Studies

When prisoners are subjects of a federally funded study, regulations in 45 CFR 46.304(b) require that at least one member of the reviewing IRB shall be a prisoner or that a prisoner representative with appropriate background and experience be appointed to serve in that capacity.

Pregnant woman or fetuses may be involved in research when: 1) pre-clinical studies, including studies on pregnant animals, and clinical studies – including studies on non-pregnant women – have been conducted and provide data for assessing potential risks to pregnant women and fetuses; and 2) the risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus, or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means (45 CFR 46.204).

When children are subjects in a federally funded study, there must be provisions made to solicit the assent of the children, when in the judgment of the IRB, the children are capable of providing assent (45 CFR 46.408). (See Chapter 4 for information on assent of children.)

and with the regulated terms of assurance. The FWA should include information identifying the institution, the components of the institution where clinical research will be conducted (e.g., research will be done in ABC Hospital and in the XYZ School of Public Health), a statement of the ethical principles to be followed (e.g., The Belmont Report), a statement of commitment to comply with 45 CFR 46, and identification of the OHRP-registered IRB responsible for research review. An FWA is effective for three years and must be renewed at the end of that time to remain in effect.[5]

Health Insurance Portability and Accountability Act

In 1996, the *Health Insurance Portability and Accountability Act (HIPAA)* was enacted in an effort to simplify health care transactions and reduce costs by encouraging health care providers to submit insurance claims electronically. Concern about the security of electronically transferred sensitive health information led to a HIPAA requirement for the development of rules to safeguard the privacy of this health information. The *Standards for Privacy of Individually Identifiable Health Information*, known as the "*Privacy Rule*," was issued in December 2000 by DHHS to implement this requirement.

The Privacy Rule established a set of national standards for the protection of health information; however, there was concern that it would have unintended effects on health care quality or access. Based on information and feedback received, DHHS identified a number of areas for modification, including uses and disclosures for research purposes. Final modifications to the rule became effective in 2003.[6]

> In enacting HIPAA, Congress mandated the establishment of Federal standards for the privacy of individually identifiable health information. When it comes to personal information that moves across hospitals, doctors' offices, insurers or third party payers, and State lines, our country has relied on a patchwork of Federal and State laws. Under the patchwork of laws existing prior to adoption of HIPAA and the Privacy Rule, personal health information could be distributed – without either notice or authorization – for reasons that had nothing to do with a patient's medical treatment or health care reimbursement. For example, unless otherwise forbidden by State or local law, without the Privacy Rule, patient information held by a health plan could, without the patient's permission, be passed on to a lender who could then deny the patient's application for a home mortgage or a credit card, or to an employer who could use it in personnel decisions. The Privacy Rule establishes a Federal floor of safeguards to protect the

> confidentiality of medical information. State laws which provide stronger privacy protections will continue to apply over and above the new Federal privacy standards.
>
> Health care providers have a strong tradition of safeguarding private health information. However, in today's world, the old system of paper records in locked filing cabinets is not enough. With information broadly held and transmitted electronically, the Rule provides clear standards for the protection of personal health information.[7]

A researcher is considered to be a health care provider covered under the Privacy Rule if the researcher furnishes health care services to individuals, including the subjects of research, and transmits any health information in electronic form.[8] Therefore, more specific consent is required from subjects participating in clinical research to give authorization for the use of protected health information.

According to 45 CFR 164.508, authorization must include:

- A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion.
- The name or other specific identification of the person(s), or class of persons, authorized to make the requested use or disclosure.
- The name or other specific identification of the person(s), or class of persons, to whom the covered entity may make the requested use or disclosure.
- A description of each purpose of the requested use or disclosure. The statement "at the request of the individual" is a sufficient description of the purpose when an individual initiates the authorization and does not, or elects not to, provide a statement of the purpose.
- An expiration date or an expiration event that relates to the individual or the purpose of the use or disclosure. The statement "end of the research study," "none," or similar language is sufficient if the authorization is for a use or disclosure of protected health information for research, including for the creation and maintenance of a research database or research repository.
- Signature of the individual and date. If the authorization is signed by a personal representative of the individual, a description of such representative's authority to act for the individual must also be provided.

The Privacy Rule identifies exceptions to the above requirements for authorization. These exceptions, found in 45 CFR 164.512(i) state

that an IRB or privacy board can allow a waiver of authorization when:

- The use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals based on:
  1. An adequate plan to protect the identifiers from improper use and disclosure.
  2. An adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.
  3. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart.
- The research could not practicably be conducted without the alteration or waiver.
- The research could not practicably be conducted without access to and use of the protected health information.

The application of HIPAA and the Privacy Rule to the conduct of clinical trials requires careful consideration. Therefore, when questions arise regarding compliance with these regulations, investigators should consult with their institutional representatives and trial sponsor. Because HIPAA and Privacy Rule regulations are enforceable by law, it is important that investigators understand the requirements.

Financial Disclosure Regulations 21 CFR 54

Conflict of interest can exist in many aspects of clinical research and occurs when someone uses his or her position for personal profit or gain. For example, an investigator who owns stock in a pharmaceutical company that manufactures an investigational product might have difficulty remaining objective when participating in a trial of the product and evaluating side effects or product effectiveness. In order to minimize or eliminate such financial conflicts of interest, regulations have been put into place regarding the disclosure of potential conflicts of interest.

Financial disclosure regulations apply to all "covered" studies of drugs, biologics, and devices used to support marketing applications (New Drug Application, Biologics License Application, or Premarket Approval). The requirement for financial disclosure does not apply to

Clinical Studies That Must Comply With Financial Disclosure Regulations

Covered clinical study means any study of a drug or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with the FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements [21 CFR 54.2(e)].

studies that are conducted under emergency use, compassionate use, or treatment use provisions.[9]

These potential **financial conflicts of interest** must be disclosed if they exist during the time the investigator is carrying out the study through one year following study completion:

- stock in the sponsoring company (USD $50,000 or greater);
- proprietary interest (e.g., patent, trademark, copyright, licensing agreement) in the product being tested;
- payment arrangements that benefit the investigator if a certain study outcome occurs;
- honoraria, gifts of equipment, or other payments of >USD $25,000 (excluding the funds provided to investigative sites to conduct the study);
- retainers for ongoing consultation.[10]

Financial disclosure regulations apply to investigators and subinvestigators who are directly involved in the treatment or evaluation of research subjects. Financial disclosure should be provided for all investigators identified in sections 1 and 6 on the Form FDA 1572 for Investigational New Drug (IND) application trials and in the Investigator Agreement for Investigational Device Exemption (IDE) trials. Financial disclosure is also required for the spouses and dependent children of all identified investigators.[11]

It is important to note that, while the existence of financial interest in a sponsoring company or product does not preclude participation of an investigator in the study, the sponsor must decide how to manage the financial conflict of interest. When an investigator with a disclosed financial interest does participate in a study, it may mean that the FDA will take a closer look at the marketing application to determine if the financial interest led to influence or bias in reporting study data. Sponsors may manage this risk by limiting investigators with financial interest to enrollment of fewer subjects or only allowing them to participate as subinvestigators. If the concern regarding the investigator's financial conflict is significant, the sponsor may decide not to use the investigator in the study.

The study sponsor is responsible for the collection of financial information from all investigators participating in a clinical trial. Sponsors usually create a database of financial disclosure information collected during the course of the trial through the one-year post-study completion period, so that it is complete and available to submit as part of the marketing application. The FDA may refuse the marketing application if certification and/or disclosure information is not included with the application.

Sponsor Reports Financial Disclosure Information to the FDA

When the sponsor determines that there are no financial conflicts of interest that need to be disclosed, *Form FDA 3454 Certification: Financial Interests and Arrangements of Clinical Investigators* should be completed and submitted to the FDA with the marketing application. However, if financial conflict of interest exists, the sponsor must include it on *Form FDA 3455: Disclosure: Financial Interests and Arrangements of Clinical Investigators*. Sponsors may also report this information on a form of their own design instead of using Forms 3454 and 3455; reporting is done at the time of marketing application.

Financial disclosure information must be collected at the beginning of a study before the investigative site can initiate trial procedures. Investigators receiving federal funds for the clinical trial must fully disclose financial and other conflicts of interest before any funding is used. If a change occurs during the study, such as the addition of new investigators or a change in the status of an existing investigator's financial conflict of interest, updated information must be provided to the study sponsor. Financial disclosure information is collected again one year after study completion (defined as study site closure).

Clinical Trials Registration

The *FDA Amendments Act of 2007* mandates registration of trials and reporting of results of applicable clinical trials in an online data bank at *www.ClinicalTrials.gov.* Trials must be registered by the sponsor or designee no later than twenty-one days after the enrollment of the first subject.

The trials that must be registered generally include: 1) *Trials of Drugs and Biologics*: Controlled, clinical investigations, other than phase 1 investigations, of a product subject to FDA regulation; and 2) *Trials of Devices*: Controlled trials with health outcomes, other than small feasibility studies, and pediatric post-market surveillance. The NIH encourages registration of all trials whether required under the law or not.[12]

Which Regulations Apply to the Trial?

It is important to understand which regulations are in effect for each specific trial. Many trials fall under both Titles 21 and 45 – Title 21 because an FDA-regulated product is under investigation and Title 45 because of federal funding for the study. Some federally funded trials fall only under Title 45; for example, an NIH-funded trial comparing two marketed products that are used in a manner that is consistent with the product labeling. A trial of an investigational product that does not receive federal funding would fall only under Title 21 regulations.

While the CFR contains the minimum requirements for the conduct of clinical research in the United States, local governments (e.g., state, county), study sponsors, and IRBs often have additional requirements. It is important to know which regulations are required by the federal and local governments because these requirements apply to all trials conducted at a specific site versus those required by the pharmaceutical company sponsoring a trial, which will vary from sponsor to sponsor.

SCD-HeFT (Prevention of **S**udden **C**ardiac **D**eath in **H**eart **F**ailure **T**rial) was an NIH-funded study. Patients with New York Heart Association Class II or III congestive heart failure and an ejection fraction <35% were randomized to one of three treatment arms – amiodarone, an implantable cardioverter defibrillator (ICD), or placebo – to determine if either of these treatments reduced the incidence of arrhythmia-related death as compared with placebo. While amiodarone had been used for 20 years and was approved for use in the treatment of life-threatening arrhythmias, its use as a preventive therapy (before a first episode had occurred) in chronic heart failure patients was investigational. ICDs had been approved for use in patients who survived a cardiac arrest but not for use in patients who had no previous episode of a life-threatening arrhythmia; therefore, the use of ICDs in this trial was investigational. As a result, the regulations that applied to this trial included those found in Title 21 for investigational drugs (Part 312) and investigational devices (Part 812) as well as Title 45 Part 46 for federally funded trials.

Guidelines

GCP guidelines are recommendations – but not legal requirements – for how clinical research should be conducted. A number of guidance documents have been written by the FDA providing suggestions for how to implement good clinical practice. In addition to the FDA-written documents, the International Conference on Harmonisation (ICH) E6 guidelines for GCP have been adopted as a recommendation for clinical trials conducted in the U.S.

ICH Guidelines for Good Clinical Practice

The European community pioneered this harmonization effort in the 1980s as European countries moved toward the development of a single market in the pharmaceutical industry. Once success was demonstrated in Europe, representatives from the regulatory and industry associations of Europe, Japan, and the United States identified the broader goal of establishing common worldwide regulations and guidelines.

At the 1990 *International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use*, a committee of representatives from industry and regulatory agencies was established. The committee's charge was to develop international standards for quality, safety, and efficacy that would promote greater harmonization of technical guidelines and to establish requirements for product registration that would prevent or reduce unnecessary duplication of testing in the development of new products without compromising safety and effectiveness. Additional goals were to increase cost efficiency through better use of resources and to minimize delays in product development. This group's work resulted in guidelines in four major categories:

1 chemical and pharmaceutical *quality* assurance,

2 *safety* in pre-clinical studies,

3 *efficacy* of clinical studies, and

4 *multidisciplinary* topics such as medical terminology and electronic standards for transmission of regulatory documents.

The guidelines for each of these categories are identified by the letters Q for quality, S for safety, E for efficacy, and M for multidisciplinary. Guidelines relevant to the conduct of research on human subjects can be found in the E guidelines; the E6 guideline pertains to Good Clinical Practice.

ICH guidelines have been partially or fully adopted by many countries. In the United States, the FDA adopted a number of ICH guidelines,

including *E6: Good Clinical Practice: Consolidated Guideline*, published in the May 9, 1997 Federal Register. E6 was adopted by the FDA as a guideline, or recommendation, for investigative sites, IRBs, and sponsors to follow rather than a legal requirement.

Differences between the Code of Federal Regulations and ICH E6 Guidelines

The CFR regulations and ICH guidelines are similar, with some differences in wording and definitions. Some of the differences relate to the written consent form:

- 21 CFR 50.25(a)(b) Elements of Informed Consent lists 8 required elements that must be included in every consent form with 6 additional or optional elements that should be included only as applicable. ICH Guidelines Section 4.8.10 Informed Consent of Trial Subjects lists 20 elements (including the 14 elements in 21 CFR) to be included in every consent form.
- ICH Guideline 4.8.11 states that the subject (or legally acceptable representative) should receive a copy of the signed and dated consent form. 21 CFR 50.27(a) requires that only the subject or representative receive a copy of the consent form – that is, the same version the subject signed but not necessarily a copy showing the signature.
- In cases where the subject or the subject's legally authorized representative cannot read, 21 CFR 50.27(b)(2) Documentation of Informed Consent requires a "short-form written consent document" to be read or presented to the subject. A witness to the oral presentation is required. There is no such requirement for a short-form written consent document in the ICH E6 guideline; item 4.8.9 Informed Consent of Trial Subjects states that if a subject or representative cannot read, an impartial witness should be present during the entire informed consent discussion, after which the subject or representative should sign and date the consent form.

Which Regulations or Guidelines to Follow?

In the example of a multi-center, multi-national clinical trial of an investigational drug, the trial would fall under CFR regulations and ICH guidelines:

- FDA/Title 21, because it is an investigational drug;
- ICH guidelines, because the sponsor requires all sites in the various countries to comply with E6: Good Clinical Practice: Consolidated Guidance rules.

Local Laws

Many cities, regions, and states in the U.S. have additional requirements for clinical research conducted within their boundaries. State and local laws supersede the federal regulations if they are more rigorous (that is, if they require additional protection for subjects) and do not introduce increased risk. Local laws may cover a broad range of clinical research topics, including, but not limited to, the

legal age of consent, requirement for children's assent, genetics research, IRBs, and protection of vulnerable subjects.

Local laws may also be created to address issues of legal guardianship and informed consent requirements. For example, protocol approval for studies conducted at Veterans Affairs hospitals in the state of Virginia must be obtained from local IRBs; the use of central or independent IRBs is prohibited. Florida requires investigators to carry a certain minimum level of malpractice insurance. In Illinois, medical records must be retained for 10 years after the most recent use for patient care.

California Local Laws

The state of California requires that all study subjects are given a copy of the *Experimental Subject's Bill of Rights*. California law also addresses the exclusion of women and minorities in clinical research and, because of California's large non-English-speaking population, requires that the consent form and Experimental Subject's Bill of Rights be written in a language in which the subject is fluent. While federal regulations require a copy of the consent form be given to each subject, California law requires that it is a copy of the actual consent form *signed by the subject*.

Experimental Subject's Bill of Rights

Any person who is asked to take part as a subject in research involving a medical experiment or who is asked to consent on behalf of another is entitled to receive the following list of rights written in a language in which the person is fluent. This list includes the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment and any drug or device to be utilized.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedures involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of the signed and dated written consent form.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.[13]

Definitions of Investigator in the Regulations

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, the responsible leader of that team [21 CFR 50.3(d); 21 CFR 56.102(h); 21 CFR 312.3(b), and 21 CFR 812.3(i)].

Investigator. A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator (*ICH Guidelines 1.34*).

Responsibilities in the Code of Federal Regulations

The regulations are a system of shared responsibilities created to conduct clinical research fairly and ethically and to protect human subjects. The regulations identify responsibilities for clinical investigators, IRBs, and sponsors.

Principal Investigator Responsibilities

An investigator is defined in the regulations as the individual who conducts a clinical investigation or, in the event of an investigation conducted by a team of individuals, the responsible leader of that team. An investigator must be qualified to oversee the conduct of a study and be thoroughly familiar with the investigational product as described in the protocol and investigator's brochure.

Responsibilities of investigators can be found in the regulations in the following sections:

IND trials:	21 CFR 312.60 through 312.69
IDE trials:	21 CFR 812.100 through 812.110, §812.140(a), and §812.150(a)

General responsibilities include, but are not limited to, conducting the study according to the protocol, obtaining IRB approval to conduct the study, obtaining informed consent from subjects before initiating study procedures, reporting adverse events, and maintaining accurate study records and test article accountability records. Investigators must also be aware of local rules and regulations for responsibilities in addition to those identified in the Code of Federal Regulations.

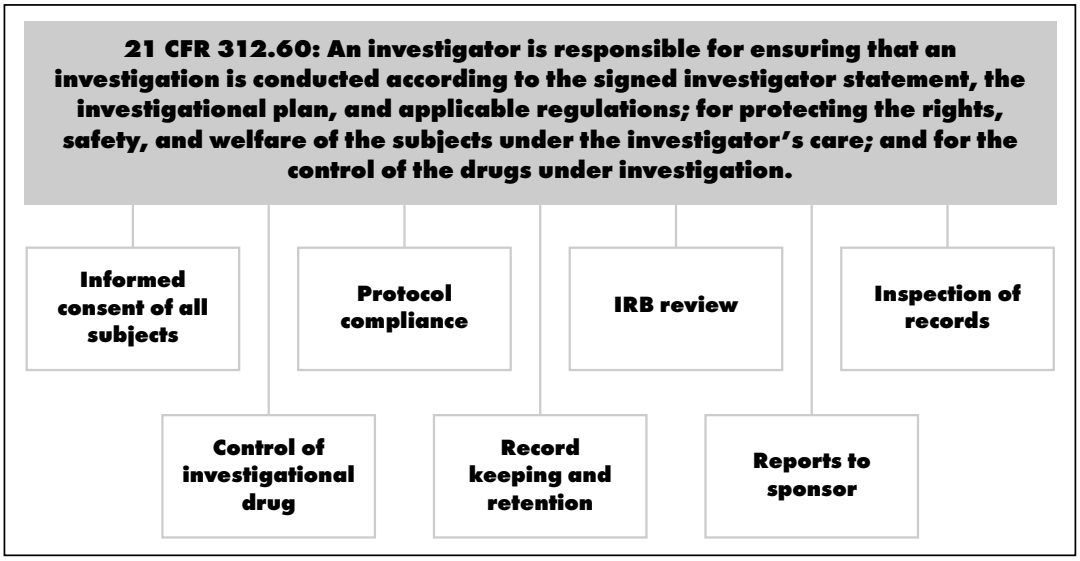
Investigational New Drug Studies

In IND studies of drugs and biologics, the principal investigator is responsible for the overall conduct of the study at the site. Before a clinical trial involving an investigational drug or biologic can be conducted, the investigator is usually asked to sign a Form FDA 1572, a contract between the sponsor and the investigator. While the signing of a Form FDA 1572 is not a regulatory requirement, the investigator has to attest to everything that is included on the form; therefore, most sponsors find the use of the Form FDA 1572 to be the easiest way for investigators to attest to these responsibilities.

When signing the required Form FDA 1572, the investigator agrees to:

1 Conduct the study in accordance with the relevant, current protocol and make changes to the protocol only after notifying the

Figure 3.1 Principal Investigator Responsibility Summary



sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

2 Personally supervise the study.

3 Inform subjects that the drugs are investigational and ensure compliance with the requirements for obtaining informed consent and IRB review and approval.

4 Report adverse experiences to the sponsor.

5 Read and understand the information in the Investigator's Brochure, including potential risks and side effects.

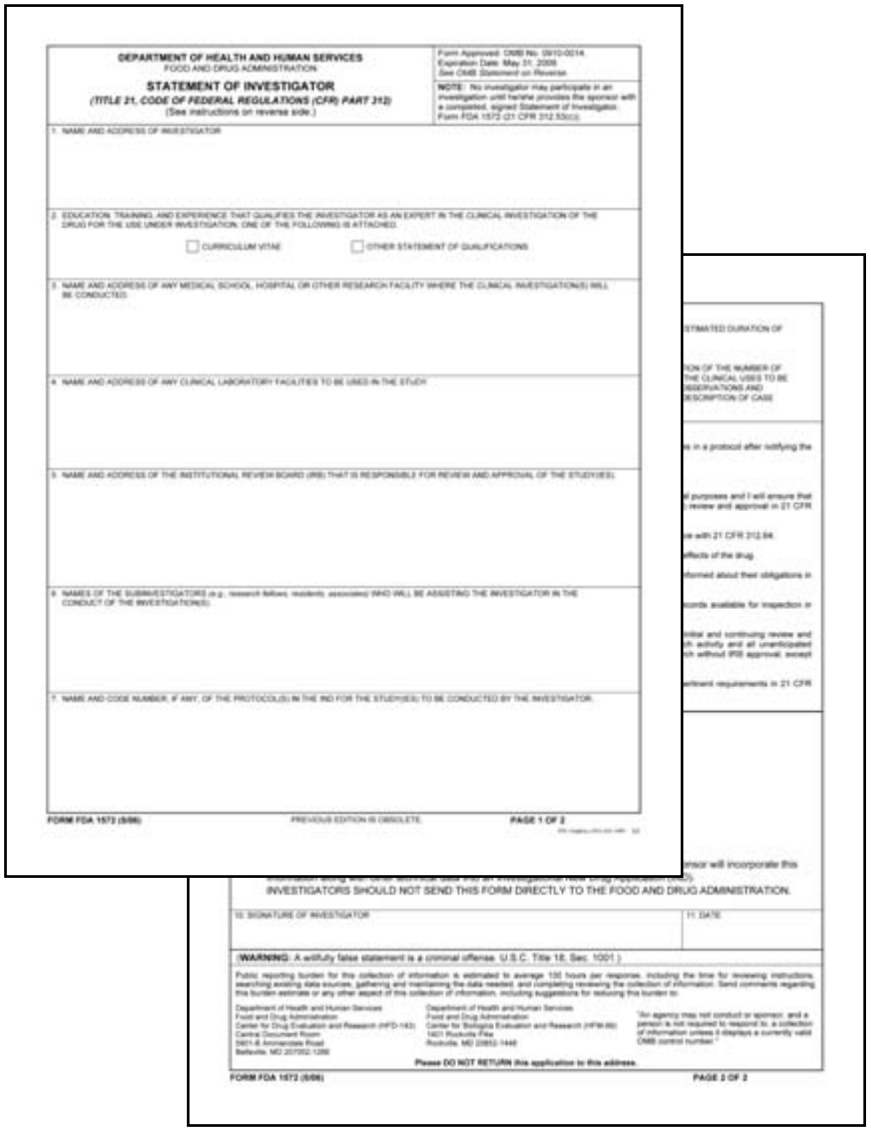
6 Ensure all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

7 Maintain adequate and accurate records and make them available for inspection.

8 Ensure that the IRB complies with its regulatory requirements; promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to subjects or others; not make changes to the research without IRB approval, except when necessary to eliminate apparent immediate hazard to subjects.

9 Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR 312.

Figure 3.2 Form FDA 1572



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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: May 31, 2006
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.

FORM FDA 1572 (5/06) PREVIOUS EDITION IS OBSOLETE. **PAGE 1 OF 2**

INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

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 150 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:

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Center for Drug Evaluation and Research (HFD-143)
Central Document Room
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Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
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Please DO NOT RETURN this application to this address.

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Investigational Device Exemption Studies

Responsibilities of investigators participating in IDE studies are similar to those of investigators in studies of drugs and biologics. Unlike IND studies, investigators participating in IDE studies do not complete a Form FDA 1572; however, much of the same information is collected by the sponsor to submit to the FDA as part of the IDE application. This contract between the sponsor and investigator is sometimes called an Investigator Agreement; sponsors may collect this information in a format of their own choosing.

By signing the agreement with the sponsor, the investigator agrees to ensure that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations; to protect the rights, safety, and welfare of subjects under the investigator's care; and to control the devices under investigation. An investigator must also comply with the informed consent requirements in 21 CFR 50.[14]

Title 21 Section 812.110 lists specific responsibilities of investigators in IDE studies:

1 While awaiting approval, investigators may determine whether potential subjects would be interested in participating but may not request the written consent of subjects or allow subjects to participate before obtaining IRB and FDA approval.

2 Investigators must conduct the study in accordance with the signed agreement with the sponsor, the investigational plan, the regulations in 21 CFR 812 and all other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

3 Investigators must supervise the use of the investigational device and may not supply the device to any person not authorized to receive it.

4 Investigators must provide financial disclosure information to the study sponsor as required in 21 CFR 54; investigators must promptly update this information if any relevant changes occur during the study and for one year following the completion of the study.

5 Investigators must return or dispose of all remaining investigational devices as instructed by the study sponsor.

General Investigator Responsibilities for Drug, Biologics, and Device Trials

Maintain professional credentials and financial disclosure

- Update CV
- Maintain expertise in clinical and research areas
- Provide financial disclosure information to sponsor

Adhere to protocol

- Instruct and personally supervise staff to ensure compliance
- Ensure that subjects meet eligibility criteria

Recruit and enroll appropriate subjects; obtain informed consent

- Ensure that selection process avoids bias
- Adhere to randomization scheme and blinding
- Obtain informed consent from all subjects before initiating study procedures

Maintain appropriate source documentation

- Ensure that medical records reflect complete subject information
- Ensure that sponsor and regulatory authorities have access to source documents as needed

Ensure data quality

- Confirm that data are complete and accurate
- Provide timely and accurate responses to data queries

Maintain drug/biologic/device accountability

- Accurately document study product receipt, dispensing, return, or destruction
- Use or administer only to subjects involved in the study; do not supply to unauthorized persons
- Provide secure locked storage of study product

Maintain proper study files and documentation

- Document personal involvement and tasks delegated to staff
- Document supervision/guidance to staff
- Maintain subject data records
- Maintain site study file and regulatory documents

Communicate with IRB

- Submit protocol, amendments, consent form, and advertising material to IRB for review and approval
- Obtain IRB approval before enrolling subjects
- Notify IRB of serious adverse events and unanticipated problems involving risks to subjects or others
- Meet IRB-required conditions for renewal
- Maintain records of all communication with IRB

Submit reports

- Provide safety reports to the IRB
- Submit progress reports/final report to IRB
- Submit progress reports/final report to sponsor

Additional Investigator Responsibilities Noted in ICH E6

In addition to investigator responsibilities identified in the CFR, ICH E6 guidelines state that investigators should have sufficient time to properly conduct and complete the trial within the agreed period of time (ICH 4.2.2), have adequate qualified staff and facilities to conduct the trial (ICH 4.2.3), and should ensure that all staff assisting with the trial are adequately informed about the protocol, the test product, and their trial-related duties (ICH 4.2.4). Investigators must ensure that adequate medical care is provided to subjects to treat trial-related adverse events (ICH 4.3.2) and should, with the subject's permission, inform the primary care physician regarding the subject's participation in the trial (ICH 4.3.3).

Institutional Review Board Responsibilities

The term *Institutional Review Board* refers to any board, committee, or other group formally designated by an institution to review, approve the initiation of, and conduct periodic review of biomedical research involving human subjects.[15] Institutional Review Board is a generic term; these committees may be called by other names, such as Ethics Committee or Independent Ethics Committee (used in the ICH guidelines). The primary purpose of the IRB review process is to ensure that the rights and welfare of human subjects are protected, both in advance and by periodic review.

Some of the IRB responsibilities for studies of drugs, biologics, and devices are:

1 Reviewing, approving/disapproving, or requiring modification of all research activities covered by the regulations.

2 Requiring documentation of informed consent in accordance with the regulations, except in cases when written consent can be waived for some or all subjects because research activities present no more than minimal risk of harm and involve no procedures for which written consent is required outside the research context.

3 Providing investigators and institutions with written documentation of approval, disapproval, and/or required modifications of all research activities.

4 Reviewing the research at least once a year in accordance with the regulations.

5 Ensuring that IRB committee membership consists of at least 5 members:

   a Of both sexes, when possible, and sufficiently qualified with different backgrounds, expertise, experience, and diversity

Additional IRB Responsibilities for IDE Trials

IRBs reviewing IDE trials must comply with the requirements of 21 CFR Part 56 as well as fulfill the additional responsibilities that are found in the device regulations in 21 CFR 812.60–66. The IRB also assesses whether a device meets the definitions of nonsignificant risk (NSR) versus significant risk (SR). This distinction is important because NSR devices are governed by different regulations and are subject to abbreviated requirements [21 CFR 812.2(b)]; sponsors are not required to submit an IDE application to the FDA or notify the FDA before starting an NSR device study. When a sponsor submits for IRB review a study investigating the use of a device that the sponsor believes to be NSR, the IRB must first determine if it is in agreement with the risk assessment. Once the IRB agrees with the NSR assessment, it can subsequently approve or disapprove the study. If the IRB disagrees with the sponsor's NSR assessment, the IRB must notify the investigator and, when appropriate, the sponsor. The sponsor must then submit an IDE application to the FDA before conducting the study. See Chapter 2 for additional information about significant risk and nonsignificant risk devices.

including consideration of race, cultural backgrounds, and sensitivity to community attitudes.

   b At least one of whom is not employed by or part of the immediate family of someone who is employed by or otherwise affiliated with the institution.

   c One whose primary concern or work is in a scientific area.

   d One whose primary concern or work is non-scientific.

6 Ensuring that any member who has a conflicting interest in a project reviewed by the IRB will not participate in the initial or continuing review of the project, except to provide information as requested by the IRB.

A full list of responsibilities can be found in 21 CFR 56.107-115 and 45 CFR 46.107-115.

When performing a review of a research protocol, an IRB:

- may invite individuals with competence in specific areas to participate in the review of complex issues beyond the expertise of IRB members, but these individuals cannot vote with the IRB;
- must conduct continuing review of previously approved protocols at intervals appropriate to the degree of risk involved in the study, but at least once a year;
- may perform expedited review of a study if there is no more than minimal risk or if the review concerns minor changes to a study that was approved in the previous twelve months.

Regulations require IRBs to have written procedures for their activities. Both the CFR and ICH guidelines require IRBs to have written procedures for:

- initial and continuing review;
- reporting IRB actions to investigators;
- determining their review schedule;
- ensuring prompt reporting to the IRB by investigators;
- ensuring that changes to research protocols are not implemented until IRB approval is given;
- maintaining records for at least three years after the completion of research.

Sponsor Responsibilities

The regulations define a sponsor as the "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."[16] Under IND regulations, sponsors may transfer any or all responsibilities by contract to a commercial or academic organization; however, any such transfer must be described in writing. The organization assuming the responsibilities transferred from the sponsor must comply with all applicable regulations and is subject to the same regulatory action as a sponsor for failure to comply.

Among the sponsor responsibilities for studies involving investigational drugs and biologics identified in 21 CFR 312.53 through 312.59 are:

1 Selecting qualified investigators (qualified by training and experience as appropriate experts to investigate the investigational product).
2 Providing investigators with information to conduct the study properly.
3 Ensuring proper monitoring (study conducted per protocol and with applicable ethical and regulatory considerations).
4 Ensuring the study is conducted according to the general investigational plan and protocols contained in the IND application.
5 Maintaining an effective IND with respect to the study and protocol.
6 Ensuring that the FDA and all participating investigators are promptly informed of significant new adverse effects/risks with respect to the drug.
7 Submitting financial disclosure information regarding the financial interests of each participating investigator.
8 Ensuring the return (or authorization of alternative disposition) of all unused supplies of the test product.

During ongoing investigations, sponsors are responsible for monitoring the progress of the study, reviewing and evaluating safety and effectiveness data, submitting annual reports to the FDA, and discontinuing studies if there is an unreasonable and significant risk to subjects. Sponsors may transfer any or all of their obligations to an academic research organization (ARO) or contract research organization (CRO); transfer of obligations must be submitted to the FDA in writing. The organization that assumes the sponsor obligations is then subject to the same regulatory action for failure to comply with the regulations.[17]

As part of the sponsor's responsibilities for ongoing review, a sponsor who discovers that an investigator is not complying with

Sponsor Responsibilities in IDE Studies

Sponsor responsibilities for device trials are listed in 21 CFR 812.40 through 812.47 and are similar to those for IND studies.

- The sponsor must obtain a signed Investigator Agreement (Form FDA 1572 is not used in device trials) from each investigator – including the curriculum vitae and relevant experience of the investigator – as well as the investigator's written agreement to conduct the study according to protocol, to oversee the use of the device, to ensure that requirements for informed consent are met, and to disclose information regarding financial conflict of interest.
- The sponsor must submit an IDE application to the FDA for significant risk device studies.
- The sponsor is responsible for selecting qualified investigators and keeping them informed about the study, ensuring proper monitoring of the study, ensuring that IRB review and approval is obtained, and ensuring that all reviewing IRBs and the FDA are promptly informed of significant new information about the study.
- Financial disclosure information for participating investigators must be submitted to the FDA with the marketing application.
- IDE regulations do not provide for a transfer of sponsor obligations to another organization; a CRO or ARO can only be a subcontractor in device trials.

the Form FDA 1572/Investigator Agreement responsibilities, the study protocol, or the regulations shall either secure compliance from the investigator or end the investigator's participation in the study. Ending the investigator's participation includes discontinuing shipment of study materials to the investigator, requiring the investigator to return remaining products, and notifying the FDA. The FDA may disqualify an investigator from clinical studies if there has been repeated or deliberate failure of the investigator to comply with applicable regulatory requirements or deliberate submission of false data. A disqualified investigator is not eligible to receive investigational drugs, biologics, or devices.[18]

Sponsor-Investigators

In some clinical trials, an individual functions as both the sponsor and the investigator. In 21 CFR 312.3(b) and 21 CFR 812.3(o), a sponsor-investigator is defined as an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational product is administered, dispensed, or used. The term is used only in reference to an individual. A sponsor-investigator must adhere to the regulations pertaining to both sponsors and investigators.

Where to Obtain Information and Guidance for the Regulations and GCP

There are a number of sources from which one can obtain information about the regulations and guidelines that apply to clinical research. These include the Federal Register and FDA guidance documents. Institutional IRBs are also a source of information regarding application of the regulations and additional requirements for local authorities.

The Federal Register

The Federal Register is the official daily publication for rules, proposed rules, and notices of federal agencies and organizations, as well as executive orders and other presidential documents. Proposed regulations and guidance documents are published in the Federal Register to give interested parties

the opportunity to review and comment on the rules before they are finalized. Reviewers may submit suggestions regarding the content and exact wording of proposed regulations, or comment on the date the proposed regulation will go into effect as well as on the penalties for non-compliance with the regulation. These comments are reviewed in a government forum. Once a regulation is made final, it is known as a "Final Rule" and is once more published in the Federal Register. Later, organized by topic or subject matter, it is incorporated into the next issuance of the Code of Federal Regulations.

FDA Guidance Documents

The FDA has written documents that provide guidance about the regulations. These documents are not legal requirements but represent the FDA's current thinking about a research-related topic. Known as "Information Sheets," these guidances provide recommendations to help IRBs, investigators, and sponsors fulfill their regulatory responsibilities to protect human subjects who participate in clinical research. *Information Sheet Guidances: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors* are arranged by subject and attempt to clarify and provide examples of ways in which the regulations can be met. These guidances provide answers to frequently asked questions about human subject protection, informed consent, review of research, and related topics. Information Sheet Guidances cover a wide range of topics, for example:

- Informed consent
- IRB operations
- Emergency use of investigational treatments
- Confidentiality
- Compensation for research-related injuries
- Medical devices studies
- Frequently asked questions

Online Resources

The Federal Register, FDA Guidance Documents, the Code of Federal Regulations, and ICH guidelines can easily be found on the Internet. The FDA Web site includes information on many FDA-related topics, including current product approvals, adverse drug reactions and device effects, FDA history, MedWatch, and recent news releases, as well as links to many other pertinent sites. A list of useful Web sites is provided in Appendix E.

References

1 www.fda.gov/oc/gcp/comparison.html
2 http://grants.nih.gov/grants/policy/hs_educ_faq.htm
3 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html
4 http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm
5 http://www.hhs.gov/ohrp/assurances/assurances_index.html
6 http://www.hhs.gov/hipaafaq/about/192.html
7 http://www.hhs.gov/hipaafaq/about/188.html
8 45 CFR 160.102, 160.103
9 http://www.fda.gov/cdrh/devadvice/ide/financial.shtml
10 21 CFR 54.2
11 21 CFR 54.2(d)
12 http://www.grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html
13 http://www.ag.ca.gov/research/pdfs/bill_of_rights.pdf
14 21 CFR 812.100
15 21 CFR 56.102(g)
16 21 CFR 56.102(j)
17 21 CFR 312.52
18 21 CFR 312.56

4 Informed Consent and the Regulations

In this Chapter

- What is informed consent?
- Ethical codes regarding informed consent
- Regulatory requirements for informed consent
- Consent from vulnerable subjects
- The informed consent process

For complete details of regulatory requirements and guidelines regarding informed consent, refer to the Code of Federal Regulations, FDA Guidance Documents, and ICH E6 Guidelines.

"No man is good enough to govern another man without that other's consent."
Abraham Lincoln (1809–1865), 16th President of the United States of America

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

1897 Yellow Fever Studies Increase Awareness of Informed Consent

History provides many instances of investigations done without informed consent. One such example took place in the late 1800s when yellow fever was one of the most feared diseases, estimated to have killed hundreds of thousands of people in periodic epidemic outbreaks. Symptoms of yellow fever ranged from self-limiting bouts of fever to severe hepatitis (the disease's name derives from the jaundice seen in some patients) and hemorrhagic fever. While working in South America, the Italian scientist Giuseppe Sanarelli claimed to have discovered that a bacterium (*Bacillus icteroides*) was the cause of yellow fever. Sanarelli injected patients with cultures of the bacillus without their permission or consent; three of the five subjects died. Responding to reports of Sanarelli's investigation, physicians and scientists were outraged. Canadian physician Dr. William Osler, considered to be the father of scientific medical practice, stated that "To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction, is not ridiculous, it is criminal."[1] Major Walter Reed, a U.S. physician and surgeon, was influenced by Osler's statement. As Reed conducted investigations into the cause of yellow fever, he obtained written consent from all of his subjects, soldiers and civilians in Cuba at the end of the Spanish-American War.[2] Reed, building on pioneering work by the Cuban physician Carlos Juan Finlay, confirmed that yellow fever was in fact not caused by the bacillus, but was spread by the bites of mosquitoes infected with a virus that caused the disease.[3]

The very nature of clinical research requires a comparatively small number of individuals to shoulder the risks of participating in investigations of unproven medical products. Researchers have the responsibility to inform subjects of these risks and to protect the rights and welfare of subjects who choose to participate in clinical trials. The informed consent process is one of the methods used to fulfill this responsibility.

What Is Informed Consent?

Informed Consent: A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.[4]

Informed consent is the process of giving potential research participants appropriate information and allowing them to make an informed and voluntary decision about study participation. After being informed of all relevant aspects of a trial, the prospective subject is given the choice of whether or not to participate in the study. Informed consent should begin before study participation and continue throughout the duration of the study (in other words, a research subject can also choose to stop participating in a study at any time, for any reason). Rather than "informed consent," a more appropriate term might be "informed decision-making," since this reflects the choices a subject can make – to give "consent" when choosing to participate or to "dissent" when choosing not to

participate. It must be made clear to potential subjects that they can choose to decline study participation without fear of repercussions, guilt, or ill will on the part of the investigator.

Ethical Codes Regarding Informed Consent

A number of codes of medical ethics emphasize the personal responsibility of physician-investigators to provide subjects with adequate and appropriate information. The Belmont Report, the Declaration of Helsinki, and the Nuremberg Code all impart principles of ethical conduct for experiments in humans. Ethical issues revolve around the safety of the participating individual rather than the community at large. Although the community may benefit from an individual's participation in clinical research, an individual should not be subjected to unreasonable harm or risk for the sake of the community.

The Belmont Report: Application of Respect for Persons

The Belmont Report, issued in 1979, is a statement of three basic ethical principles for the protection of human research subjects. The first is *Respect for Persons*, and application of this principle occurs as part of the informed consent process. Respect for persons requires investigators to acknowledge subjects as autonomous persons, capable of understanding and making judgments for self-determination. This principle also requires investigators to recognize that some individuals are not or cannot be autonomous, and therefore need additional protection. Diminished autonomy may occur at different times, such as during childhood when immaturity prevents the child from making informed decisions, or during an illness when an individual may be temporarily unable to understand and make informed choices. Diminished autonomy may also be a permanent or persistent condition, as in individuals with cognitive impairment from birth or because of injury.

In order to allow subjects to make an informed decision about participating in clinical research, the informed consent process must be based upon three components: 1) information, 2) comprehension, and 3) voluntariness.[5] First, subjects should be given sufficient information regarding the investigational therapy, the purpose of the study, potential risks and benefits of the therapy, alternative

Informed consent is based upon three components:

1. giving information about the proposed research study;
2. ensuring comprehension of that information; and
3. requesting voluntary participation.

therapies or drugs, and any other information necessary to make an informed decision. Second, information must be presented in ways that the subject can readily comprehend. This requires the investigator to present information in an organized, unhurried manner, allowing enough time for the potential subject to consider the information and ask questions. The information must also be presented at an appropriate level of complexity and in a language that can easily be understood by the individual. Last, consent is only valid when it is given voluntarily. The component of voluntariness prohibits the use of undue influence (i.e., excessive or inappropriate reward to obtain compliance) or coercion (i.e., intentional threat of harm to obtain compliance).

In situations where the investigator is the subject's physician and the subject depends upon the physician to make all decisions regarding health care, it can be difficult to obtain truly informed and voluntary consent. In such a situation, it is advisable to have someone other than the physician-investigator lead the discussion about the study. Investigators must be extremely careful to avoid exerting undue influence in the informed consent process.

The Declaration of Helsinki

Originally written in 1964 at a meeting of the World Medical Association (WMA), the Declaration of Helsinki is a statement of ethical principles to guide physicians in clinical research. The declaration is prefaced with a binding statement for physicians: "The health of my patient will be my first consideration."

The Declaration of Helsinki includes several principles related to informed consent, including:

1 Subjects must be volunteers and informed participants.

2 Subjects must be adequately informed, which includes being told of the right to choose not to participate or to withdraw consent at any time without reprisal.

3 Physicians should be particularly cautious when approaching patients who are dependent upon the physician for decision making regarding health care; it is advised that an independent physician approach the patient for consent.

4 When subjects are not autonomous or capable of giving informed consent, consent must be obtained from a legally authorized representative.

5 Assent should be obtained from children in addition to consent from the legally authorized representative.

The Nuremberg Code

The Nuremberg Code, developed as a method for judging Nazi physicians who conducted abusive biomedical experiments during World War II, contains 10 standards or conditions, which became the prototype for ethical codes governing the conduct of experiments on humans. The first standard makes a strong statement regarding the requirement for voluntary consent, holding the investigator directly responsible:

> The voluntary consent of the human subject is absolutely essential.
>
> This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment.
>
> The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.[6]

During the trial of Nazi physicians held at Nuremberg in 1946, fundamental ethical standards for the conduct of human research were documented in the Nuremberg Code, which set forth ten conditions that must be met to justify research involving human subjects. One of the most important conditions was the need for voluntary informed consent from subjects.

In 1972 it came to the public's attention that, since 1932, approximately 400 African-American men who had syphilis had been studied, without their knowledge, to observe the natural course of the disease. In this study, performed in **Tuskegee**, Alabama, subjects were denied treatment with penicillin, which was known to cure syphilis, to allow researchers to follow the progression of the untreated disease.

Regulatory Requirements for Informed Consent

In addition to these ethical codes of conduct, the U.S. Code of Federal Regulations (CFR) contains requirements that govern how consent may be obtained from study participants. Two historical events primarily responsible for shaping current regulations are the medical experiments performed on prisoners of war during World War II and the Tuskegee Syphilis Study conducted under the U.S. Public Health Service from 1932 to 1972.

Regulations have since been implemented to ensure that all future study participants are given sufficient information about the study, study procedures, and alternative treatment, and allowed to choose

freely whether or not to participate. The regulations also require that information be presented in a manner and at a level of complexity that prospective subjects can comprehend.

Informed consent regulations found in CFR Title 21 (Part 50, Subpart B) and CFR Title 45 (Parts 46.116 and 46.117, and Subparts B, C, D), and guidelines found in the International Conference on Harmonisation (ICH) E6 Guidance for Good Clinical Practice (Section 4.8), are intended to safeguard the rights and welfare of subjects participating in clinical research and are applicable to studies of drugs, biologics, and medical devices. Informed consent must also be obtained when studies do not involve the use of a medical product, but are conducted to solicit private health information from subjects, such as the administration of questionnaires, the retrospective review and recording of medical record data, or comparison of activities (e.g., comparison of exercise versus meditation). As is evident in the regulatory responsibilities for investigators, Institutional Review Boards (IRBs), and sponsors (Chapter 3), all three groups are responsible for ensuring the ethical conduct of a study, which includes informed consent.

Coercion occurs when an overt or implicit threat of harm is intentionally presented in order to obtain compliance. For example, an investigator might tell a prospective subject that the subject will lose access to needed health services if he does not agree to participate in the research.

Undue influence, by contrast, often occurs through an offer of an excessive or inappropriate reward in order to obtain compliance. For example, an investigator might promise psychology students extra credit if they participate in the research study. If that is the only way a student can earn extra credit, then the investigator is unduly influencing the students as potential subjects. If, however, the investigator offers comparable non-research alternatives for earning extra credit, the possibility of undue influence is minimized.[7]

General Requirements for Informed Consent (21 CFR 50.20)

The regulations contain a number of general requirements for obtaining informed consent from human subjects. These requirements can be found in 21 CFR 50.20, 45 CFR 46.116, and ICH E6, Section 4.8. The following list summarizes the general requirements of informed consent in 21 CFR 50.20:

1. No investigator may involve a human subject in a clinical trial unless legally effective informed consent has first been obtained, except as provided in 21 CFR 50.23 and 50.24 (see Exceptions on the opposite page).
2. The subject or the subject's legal representative must be provided sufficient opportunity to consider whether or not to participate, without coercion or undue influence.
3. Information presented to the subject must be in language understandable to the subject or representative (as determined by the IRB and local community needs).
4. No consent form may include exculpatory language through which the subject or legal representative waives or appears to waive any legal rights or releases or appears to release the investigator, sponsor, the institution, or its agent from liability for negligence.

Exceptions from the General Requirements (21 CFR 50.23)

There are some situations in which waiving the general requirements for informed consent can be justified. Regulations in 21 CFR 50.23 permit the waiving of the general requirements for consent for certain individuals whom an investigator believes would benefit from the investigational product, but who are not capable of consenting to participate in the study.

In such a case, **all four** of the following conditions must be true:

- The subject is confronted by a life-threatening situation and administration of the test article may save the subject's life.
- Informed consent cannot be obtained because of the subject's inability to communicate or give consent.
- There is not sufficient time to obtain consent from the subject's legal representative.
- There is no alternative treatment available that is likely to provide an equal or greater chance of saving the subject's life.

These four conditions must be certified in writing by the investigator as well as by a physician who is not participating in the study. Written certification must be submitted to the IRB within five working days after investigational treatment was administered. [21 CFR 50.23(b)]

Individual Exceptions: Exceptions from the general requirements for informed consent require written certification to be submitted to the IRB no more than 5 working days AFTER the administration of the investigational product to a subject.

Emergency Research Exceptions: The IRB responsible for the review of the investigational research may approve the study without requiring that informed consent be obtained from all research subjects.

Exceptions from Informed Consent Requirements for Emergency Research (21 CFR 50.24)

Some clinical trials investigate treatment of subjects in life-threatening situations where treatment must be provided quickly, patients are unconscious or otherwise incapacitated, and it is not possible to locate a legally authorized representative. This might include clinical trials of subjects with cardiac arrest, stroke, spinal cord injury, and poisoning. In these situations, the time between arrival at a hospital and initiation of treatment must be short in order to provide the greatest health benefit to the patient; delaying treatment to obtain consent could result in serious consequences, including death, for the subject.

In these trials, there is more than minimal risk to subjects, but a waiver may apply if there is a prospect of direct benefit to subjects. A waiver may be allowed if the following conditions are met:

- the study could not practicably be carried out without the waiver;

The **MAGIC** (**Mag**nesium **I**n **C**ardiac Arrest) trial was conducted at Duke University Hospital. Eligible patients were at least 18 years of age and had been treated by the hospital code team for cardiac arrest, defined as the cessation of cardiac mechanical activity confirmed by the absence of consciousness, spontaneous respiration, blood pressure, and pulse. Subjects were randomized to receive a dose of magnesium or placebo after cardiac arrest. In accordance with regulations, the Duke IRB approved the MAGIC investigation without requiring that informed consent be obtained prior to treatment.

The IRB's decision to approve an exception to the informed consent requirements was based on the following: unconscious patients are not able to give consent, the delay required to obtain consent from family members would diminish the treatment's potential efficacy, eligible patients could not be reliably identified before cardiac arrest, and the research project was deemed to be in the patients' best interest and reasonably comparable to available interventions. These patients were in a life-threatening situation, available treatments were unsatisfactory, and clinical investigation was required to determine the efficacy of the treatment.

- a therapeutic window is defined, and the researcher commits to trying to locate a surrogate/legally authorized representative who can give consent within that window before proceeding to waive consent;
- the study and consent form (to be used when possible) have IRB approval;
- consultation with community representatives occurs before the study starts; and
- public disclosure to the community is made before and after the study.

The IRB is responsible for ensuring that procedures are in place to inform subjects about the details of the study as soon as possible. If a subject remains incapacitated, the legally authorized representative must be informed that the subject was enrolled in the study or, in cases when there is no legal representative, a family member must be given the information. The subject, the legally authorized representative, or the family member should also be told of the subject's right to withdraw from the study at any time.

In addition to approving exceptions for documenting informed consent prior to administering an investigational therapy, an IRB is authorized to waive the requirement for written informed consent when it determines that a study presents no more than minimal risk to subjects (see the reference to 21 CFR 56.109(c) later in this chapter).

Elements of Informed Consent (21 CFR 50.25)

The Code of Federal Regulations identifies eight "basic" elements that must be included in every consent form, as well as six "additional" elements that must be included when appropriate.

The elements from 21 CFR 50.25 are summarized below. These required elements are based on the following ethical considerations:

- Participation in a clinical trial should be voluntary and potential subjects should not be pressured to participate.
- Subjects should be allowed to withdraw from the study without penalty.
- Subjects should be capable of making a rational decision to participate.
- Subjects should be reasonably informed, although they need not understand all the scientific principles pertaining to the study.

- Certain categories of subjects are considered vulnerable and require special consideration as to whether they are capable of giving rational informed consent to participate. Subjects considered to be vulnerable include prisoners, infants and children, pregnant women, fetuses, and cognitively impaired persons.

Synopsis of Elements in 21 CFR 50.25

Basic Elements	Additional Elements
1. Statement that study involves research and explanation of purposes, expected duration, and procedures	1. Statement that unforeseeable risks to subject, embryo, or fetus may exist
2. Description of reasonably foreseeable risks or discomforts	2. Circumstances in which subject participation may be terminated by the investigator
3. Description of benefits	3. Any additional costs to subjects that will result from study participation
4. Alternative procedures or courses of treatment	4. Consequences of and procedures for withdrawal (e.g., tapering drug dose)
5. Description of confidentiality of records	5. Statement that subjects will be informed about significant new findings that might affect subject's willingness to continue participation
6. Explanation of compensation and medical treatment for injury occurring during study	6. The approximate number of subjects participating in the study
7. Contact persons for study questions and research-related injury	
8. Statement that participation is voluntary and that there is no penalty or loss of benefits for refusal to participate	

Whereas the CFR identifies these 8 basic and 6 additional elements of informed consent, the ICH E6 Guideline identifies 20 essential elements of informed consent. Section 4.8.10 of ICH E6 requires that both the informed consent discussion and the written consent form, as well as any other written information provided to subjects, should include explanations of the elements in the list below:

Synopsis of Required Elements in ICH E6

1. The trial involves research
2. The purpose of the trial
3. Trial treatments and probability for random assignment to each treatment
4. Trial procedures
5. Subject's responsibilities
6. Experimental aspects of trial
7. Reasonably foreseeable risks
8. Reasonably foreseeable benefits (when there is no intended benefit, this should be stated)

9. Alternative treatments or course of therapy
10. Compensation and treatment in event of study-related injury
11. Payment to subject for participation
12. Anticipated expenses to subject because of study participation
13. Participation is voluntary and subject may refuse to participate or withdraw consent at any time without penalty or loss of benefits
14. Study personnel (monitors, auditors, IRB, regulatory authorities) will have access to subject's medical records for data verification without violating confidentiality; the signed written consent form provides authorization for this access
15. Records identifying the subject will be kept confidential; if results are published, subject's identity will remain confidential
16. Information relevant to continued study participation will be provided to the subject in a timely manner
17. Name and number of person the subject can contact for information regarding the rights of study subjects and trial-related injury
18. Circumstances in which the subject may be prematurely withdrawn from the study
19. Expected duration of the subject's participation
20. Approximate number of subjects involved in the study

Waiver of Informed Consent Requirement

Per 21 CFR 56.109(c), an IRB shall require documentation of informed consent in accordance with §50.27, except that 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. In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

Documentation of Informed Consent (21 CFR 50.27)

Informed consent must be documented in a written consent form approved by the IRB, as described in 21 CFR 50.27. The consent form must be signed by the subject or the subject's legal representative (as defined by each state) and a copy given to the person signing the form.

Except as provided in 21 CFR 56.109(c), the consent form may be either:

1 A written consent form that includes the basic and applicable additional elements of informed consent. The form may be read by the subject or representative, or read to the subject or representative if appropriate.

Or in specially-approved circumstances:

2 A "short form" written consent document that states that the elements of informed consent have been presented orally to the subject or representative. When this method is used, there must be a witness to the oral presentation and a written summary of what is said.

Written Consent Forms

To comply with the CFR, the written consent form must contain the eight basic elements of informed consent and all of the additional

elements of informed consent that are applicable (see Appendix C for a sample consent form). When adhering to the ICH E6 guideline for Good Clinical Practice, the consent form must contain all 20 elements identified in Section 4.8.10. When a subject agrees to participate, the subject or subject's legal representative must sign the consent form indicating willingness to participate in the study. All regulations require a copy of the consent form to be given to the subject. However, the regulations in the CFR do not require that the subject be given a photocopy of the original form containing the subject's signature (it can be an unsigned copy of the same consent form). On the other hand, the ICH E6 guidelines, the regulations regarding authorization for use of protected health information covered by the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA), as well as some states and local IRBs do require that the copy of the consent form copy given to the subject include the subject's signature. The best practice is to give subjects a copy of the consent form with their signature; this can serve as a reminder to subjects that they did sign the consent form agreeing to study participation.

Short Form and Written Summary

While not appropriate for most clinical trials, an IRB-approved *Short Form* is an alternative to the traditional written consent form in a few situations. Short forms are typically used in trials in which study subjects are acutely ill patients. Since it is unlikely that an acutely ill patient who is experiencing severe pain or other significant symptoms could carefully read and consider all the aspects of study participation, the short form presentation is an appropriate alternative to the written form. In such situations, when time-to-treatment is especially critical, the informed consent process can be fulfilled by reviewing the pertinent aspects of the study identified on the written summary associated with the study short form.

The *Short Form* briefly states that the elements of informed consent have been orally presented to the subject or the subject's legal representative. When a short form is used, there must be an impartial witness to the oral presentation to verify that all required elements of informed consent were presented. A short form must be approved by the IRB before use and signed by both the subject and the witness.[8]

A *Written Summary* of the information to be given to the subject must also be approved by the IRB when a short form is used. When discussing study participation with a potential subject, information should not be given extemporaneously or from memory. The individual presenting the information to the subject or representative

Figure 4.1 Sample Short Form

HEAT
Hypothetical Example of A Trial

Consent to Participate in a Research Study: Short Form

Study Name: **HEAT (Hypothetical Example of A Trial)**

Protocol Number XYZ 39-90213

Date: **July 19, 2009**

Sponsor: Pharmaceutical Company, USA

Principal Investigator: _____

Institution: _____

I give my consent to participate in this research study that is being done to compare an investigational clot-dissolving medicine to one already on the market. All the items on the Written Summary have been explained to me in the presence of a witness. These include the background and purpose of the study, the procedures required for the study, possible risks and benefits, alternative treatment if I do not participate, confidentiality of my records, compensation, and the names of those I should contact if I have any questions. It has been explained that it is up to me to decide if I want to participate in the study. If I do participate, pertinent new information will be explained to me while I am in the study. I have had the chance to ask questions and they have all been answered so that I understand. I have been told that a copy of this consent form and a copy of the written summary will be given to me.

_____	_____	__/__/__
Name of Study Participant	*Signature of Study Participant*	*Date*

I have witnessed the summary information being verbally presented to the subject. I confirm that all of the information in the written summary has been completely and accurately explained. The subject was given time to ask questions and the questions were answered so that the subject could understand. The subject voluntarily agreed to participate in this study and signed/marked this consent form.

_____	_____	__/__/__
Name of Witness	*Signature of Witness*	*Date*

	Short Form	Written Summary
IRB	Must approve	Must approve
Subject	Must sign; receives a copy	Does not sign; receives a copy
Person obtaining consent	Does not sign	Must sign
Witness	Must sign	Must sign

should use the written summary while orally presenting the study to ensure that the same information is presented to all potential subjects, and that all points are reviewed. Both the person presenting the information and the witness to the presentation must sign the written summary, and the subject or representative must be given a copy of both the short form and the written summary.

Consent from Vulnerable Subjects

Certain groups of subjects are considered to be vulnerable and require special protection to ensure their rights and safety. People are considered vulnerable when they have a limited ability to protect their own interests and safety. The regulations identify vulnerable subjects as those who cannot give signed or verbal consent, such as young children, cognitively impaired persons, or unconscious patients, as well as people in other special situations, such as pregnant women and prisoners. Persons with mental disorders, mental illness, and terminal illnesses may also be considered vulnerable and in need of greater protection.

The Belmont Report contains a discussion of the issues related to the vulnerability of certain persons. The report recognizes that injustices to individual subjects can arise from social, racial, sexual, and cultural biases institutionalized in society, even when individual researchers treat their research subjects fairly, and even though IRBs take care to assure the fair selection of subjects. The following excerpt from the Report provides insight into the issue of vulnerability:

> One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is

Figure 4.2 Sample Written Summary of a Research Study

HEAT
Hypothetical Example of A Trial

Written Summary

1 Since your doctorhas determined that you are having a hear tattack, you are being asked to participate in this research study.

2 Your participation is completely voluntary and if you decide to participate, you may withdraw your consent at any time without jeopardy to your medical care.

BACKGROUND AND PURPOSE OF STUDY

3 This study is being done to see if an investigational clot-dissolving medicine is as good as or better than a similar medicine already on the market, when given to people having a heart attack.

4 By quickly dissolving the blood clot in the arteries to the heart, the blood flow can resume and may reduce the amount of heart damage.

5 Approximately 5000 people in the United States will be enrolled in this study.

PROCEDURES

6 You will be given a dose of either the investigational clot-dissolving medicine or the medicine already in use for people with heart attacks. You have a 50% chance of getting the investigational medicine.

7 The medicine is prepared so that neither you nor your doctors know which medicine you are given.

8 The medicine will be given through your veins over one hour.

9 You will have your blood drawn before the medicine is given and again each morning that you are in the hospital. About 2 tablespoons of blood will be drawn each time.

POSSIBLE RISKS

10 All medicines that dissolve blood clots can cause internal bleeding. This could include bleeding into your brain, causing a stroke, which occurs in less than1% of people who get clot-dissolving medicine.

11 If bleeding is severe, you may need a blood transfusion.

12 There could be side effects that we currently do not know about.

POSSIBLE BENEFITS

13 If you get the investigational medicine, it could prove to be better at dissolving the blood clot and getting the blood flowing back to your heart.

14 The marketed medicine dissolves blood clots in about 70% of people who receive it.

ALTERNATIVE TREATMENT

15 If you are not in the study, you will probably be given the marketed medicine for your heart attack.

CONFIDENTIALITY

16 Information about you and how you responded to the treatment will be recorded on forms but your name and other information identifying you will not be written on the forms.

17 The FDA and other personnel from the company who makes the investigational medicine may review your medical records to confirm the information written on the forms.

COMPENSATION

18 You will not receive money or any other kind of compensation or reward for being in the study.

19 You will receive the clot-dissolving medicine and the blood tests required for this study for free; you or your insurance will be billed for the rest of your hospital charges.

20 If you have an injury because of being in this study, you will receive free medical care for the injury.

CONTACTS

21 If you have any questions about the study, you should call Dr. Knowledgeat (888) 111-2222. If you have any questions about your rights as a participant in a research study, you should call Ms. Answers, the chairperson of the hospital committee that reviews research studies, at (888) 333-4444.

OTHER

22 If your doctor or the company that makes the investigational medicine thinks your health or safety could be harmed if you continue in the study, your participation will be stopped.

23 While you are in the study, you will be told about any new information that might make you change your mind about participating in the study.

SIGNATURES

I confirm that the information in this written summary has been verbally presented to the subject and that consent to participate has been freely given by the subject.

_____
Name of Witness

_____ __/__/__
Signature of Witness Date

_____
Name of Person Obtaining Consent

_____ __/__/__
Signature of Person Obtaining Consent Date

> conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.[9]

The ICH E6 guideline acknowledges the vulnerability of a broad range of subjects, including those who are subordinate members of a hierarchical group. The definition of vulnerable subjects in the ICH E6 guideline on Good Clinical Practice Glossary, item 1.61 is:

> Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Applicable Regulations for Vulnerable Subjects

Specific regulations regarding informed consent for vulnerable groups of subjects can be found in the Title 45 and Title 21 of the CFR.

- Title 45, Part 46, Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved In Research
- Title 45, Part 46, Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Title 45, Part 46, Subpart D – Additional Protections for Children Involved as Subjects in Research
- Title 21, Part 50, Subpart D – Additional Safeguards for Children in Clinical Investigations

Pregnant Women, Human Fetuses, and Neonates

Historically, women of childbearing potential and pregnant women have been excluded from clinical trials because of concern regarding risks to the woman, her reproductive capability, and the unborn

fetus. However, since it is known that women metabolize some drugs differently from men, the importance of including women in clinical trials to determine safety and efficacy has been recognized.

While some studies will exclude pregnant women and/or women of child-bearing potential, others will include these women in the eligible subject population. The protocols for these trials should provide information regarding risks, guidelines regarding pregnancy testing, and a description of acceptable contraceptive methods so that women can avoid pregnancy during the trial.

The following is an excerpt of some of the regulations in Title 45 Part 46, Subpart B regarding pregnant women or fetuses involved in research. Some of the requirements are that pregnant women or fetuses may be involved when:

1 Pre-clinical studies on pregnant animals and clinical studies including women as subjects have been done to assess potential risks.

2 The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or fetus, or if no prospect of benefit, there is not greater than minimal risk to the fetus.

3 Any risk is the least possible for achieving study objectives.

4 No inducements, monetary or otherwise, can be offered to terminate a pregnancy.

5 The individuals engaged in research have no part in determining the viability of a neonate.

Investigators should refer to federal regulations and state laws for complete information regarding women as vulnerable subjects.

Prisoners

Prisoners who participate in research are particularly susceptible to undue influence and coercion because of their incarceration. The regulations require that when prisoners are involved as subjects in clinical trials, the IRB must have at least one member who is either a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity, and that no other members of the IRB may have any association with the prison involved in the study [45 CFR 46.304(a)(b)]. Other requirements in 45 CFR 46.305 include:

1 The risks involved must be commensurate with the risks accepted by non-prisoner subjects.

2 Procedures for subject selection within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners.

3 There must be assurances that parole boards will not take study participation into account when deciding parole status.

4 Participating prisoners are not awarded special advantages (medical care, living conditions, food, amenities) that would represent undue influence.

5 The information must be presented to potential subjects in a language they can understand.

When a study targets a population that includes persons with a greater likelihood of being jailed during a study, such as parolees or substance abusers, the protocol should include provisions for the procedures to follow when a study subject is incarcerated. While it is not always possible to anticipate the incarceration of a research subject, if this does occur, the investigator must contact the IRB to determine whether the subject can remain in the study and, if so, what steps need to be taken.

Children and Minors

In recent years, the FDA has required sponsors who submit marketing applications to conduct clinical trials in the pediatric population to ensure safety and efficacy in this group. For some medical products, the FDA will give marketing approval dependent on the sponsor's agreement to conduct phase 4 trials to evaluate the drug, biologic, or device in the pediatric population. While this research is important for obtaining accurate data regarding use of the medical product in children, careful consideration must be given to the risks children will face when participating in the trial.

The definition of "child" may vary from state to state, but in general, children are individuals who have not reached the age of 18, the legal age used by most states in the U.S. when individuals are allowed to authorize consent for themselves. Some states acknowledge special circumstances for individuals, such as emancipated minors, who are under 18 years of age. Because of their independent status, emancipated minors are legally allowed to consent for treatments or procedures involved in research. It is important to be aware of and understand applicable state laws regulating the inclusion of children and minors in research. The investigator must also ensure that when a minor is approached for consent, the minor possesses the mental capacity to understand the risks, benefits, and the consequences of choosing to participate in research.

Emancipated minors – those who are either:

- married or divorced; or
- on active duty in the US armed forces; or
- emancipated by a court.

have the legal right to consent on their own behalf to medical, dental, or mental health treatment. They also have extensive other rights to enter into legal and business arrangements, and so can consent to be included in other research. (California Family Code. Emancipation of Minors Law: Sections 7000–7002)

Assent From Children and Permission From Parents

When children are subjects in a clinical trial under Title 45 Part 46, consent – or permission – for the child to participate is required from

Assent means that the child agrees to participate even though he or she may not understand all the specific information concerning the study.

the parent or legal guardian. This may also be required in non-federally funded trials based on sponsor and/or IRB requirements and local laws. IRBs generally require investigators to obtain the *permission* of one or both parents or guardian and the *assent* – or agreement – of children who possess the intellectual and emotional ability to understand the concepts involved. Older children may be familiar with signing documents through previous experience with testing, applying for a driver's license, or obtaining a passport, while younger children may never have had the experience of signing a document. For this reason, some IRBs require two forms: one that fully explains the study procedures for parents and older children, and a second one that is shorter and simpler for younger children.

It is the responsibility of the IRB reviewing the protocol to determine if assent is required. The IRB will inform the investigator of additional requirements unique to children participating in research, including whether a separate form that outlines the study in simplified language is needed.

HIPAA Authorization

Investigators must obtain permission from study subjects before using their protected health information (PHI). This may be accomplished through a separate authorization form or may be included in the consent form for the clinical trial. Consent forms containing the required authorization elements are considered "HIPAA compliant." Individual research sites choose whether to include authorization elements within the consent form or to have a separate authorization form. At some sites this may be determined by the institution while at other sites it may be decided by the IRB; the state may also mandate use of one approach over another. When PHI authorization is included in the study consent form, it must be reviewed and approved by the IRB.

HIPAA/Privacy Rule Requirements

The *Health Insurance Portability and Accountability Act (HIPAA)* was enacted to simplify health care transactions and lower costs by encouraging health care providers to submit insurance claims electronically. Concerns about the security of this information led to a HIPAA requirement that rules to safeguard the privacy of this health information be developed. The *Standards for Privacy of Individually Identifiable Health Information*, known as the *Privacy Rule*, was issued in December 2000 by the Department of Health and Human Services (DHHS) to implement this requirement. When concern was expressed that the Privacy Rule would have a negative impact on access to records and thus affect health care quality, modifications were made and the resulting Privacy Rule went into effect in April 2003.

The impact of the Privacy Rule on research is to require more specific consent from subjects regarding the use of protected health information in clinical trial reporting. Regulations pertaining to this can be found in 45 CFR 164.508(c). The requirements for consent forms (authorization) in clinical trials include core elements, statements, plain language, and that a copy of signed authorization form is given to the subject. In research, the "covered entity" refers to the investigator.

Core Elements

A valid authorization must contain at least the following elements:

1 A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion.

2 The name or other specific identification of the person(s), or class of persons, authorized to make the requested use or disclosure.

3 The name or other specific identification of the person(s), or class of persons, to whom the covered entity may make the requested use or disclosure.

4 A description of each purpose of the requested use or disclosure. The statement "at the request of the individual" is a sufficient description of the purpose when an individual initiates the authorization and does not, or elects not to, provide a statement of the purpose.

5 An expiration date or an expiration event that relates to the individual or the purpose of the use or disclosure. The statement "end of the research study," "none," or similar language is sufficient if the authorization is for a use or disclosure of protected health information for research, including for the creation and maintenance of a research database or research repository.

6 Signature of the individual and date. If the authorization is signed by a personal representative of the individual, a description of such representative's authority to act for the individual must also be provided.

Statements

A valid authorization must contain at least the following statements:

1 the individual's right to revoke the authorization in writing, and either:
   - the exceptions to the right to revoke and a description of how the individual may revoke the authorization; or
   - a reference to the covered entity's notice.

2 the ability or inability to condition treatment, payment, enrollment or eligibility for benefits on the authorization, by stating either:
   - the covered entity may not condition treatment, payment, enrollment or eligibility for benefits on whether the individual signs the authorization; or
   - the consequences to the individual of a refusal to sign the authorization when the covered entity can condition treatment, enrollment in the health plan, or eligibility for benefits on failure to obtain such authorization.

Plain Language

A definition of plain language is provided by Professor Robert Eagleson of Australia: "Plain English is clear, straightforward expression, using only as many words as are necessary. It is language that avoids obscurity, inflated vocabulary and convoluted sentence construction. It is not baby talk, nor is it a simplified version of the English language. Writers of plain English let their audience concentrate on the message instead of being distracted by complicated language. They make sure that their audience understands the message easily." Readers can find a number of useful online resources, including the Web page "Improving Communication from the Federal Government to the Public," available at plainlanguage.gov. Tips include:

- Replace complex words with simpler words to let readers concentrate on the content. Save longer or complex words for when they are essential.
- Avoid the use of foreign words, jargon, and abbreviations that detract from the clarity of the writing.
- Understand your readers and match your language to their needs.[10]

3 the potential for information disclosed according to the authorization to be subject to redisclosure by the recipient and no longer be protected by this subpart.

Plain Language

The authorization must be written in plain language.

Copy to the individual

A valid authorization requires subjects to be given a copy of the authorization form, or a copy of the study consent form, when authorization is included as part of the study informed consent document. If a researcher (the covered entity) seeks an authorization from an individual for a use or disclosure of protected health information, the researcher must provide the individual a copy of the signed authorization.[11]

The Informed Consent Process

It is important to understand that informed consent is a process; that is, it is not a single discussion between an investigator and a subject, or the piece of paper known as a consent form. This process begins with the development of a written consent form and other applicable written materials. These may include such documents as advertisements for the study and educational materials to be provided to subjects. After IRB approval of the study and all written materials, the investigator may approach prospective subjects about study participation. The investigator (or other study team member) should provide the prospective subject with a written consent form and engage the subject in a discussion about the trial. Subjects should be given adequate time to read the consent form and re-read it if necessary, and have the opportunity to ask questions.

Writing the Consent Form

The written consent form plays an important role in the informed consent process. It serves as a written summary of the information

presented to the subject and is a useful tool for subjects to refer to throughout the study. The consent form also includes information regarding the subject's rights as a research participant and whom to contact if the subject has questions. The consent form needs to provide comprehensive study information, be in a language understandable by the subject, and contain all the elements required in applicable regulations.

Deciding what information and how much detail should be provided in the consent form can be quite challenging. Some clinical trials are very complex, resulting in a lengthy form. As a general rule, consent forms should be written at a level that a 10 to 12 year-old can understand (i.e., at about an eighth-grade reading level). Exceptions to this could occur when study subjects belong to a group with a higher level of education, such as a study of clinical depression in law students.

When writing a consent form, there are several considerations to keep in mind:

- In general, it should be written at an eighth grade (or lower) reading level. The information should be as simple as possible so that it can be easily understood.
- Lay language should be used instead of medical terms when possible. For example, use *"low blood pressure"* instead of *"hypotension"* and *"through the vein"* instead of *"intravenous."*
- Write in second person, using *"you."* This makes the written consent form sound the same as when the investigator is speaking to the subject. One suggestion is to write the information in sections with headers written in first person questions, and the answer in second person. For example, the header is written in first person: *"What will happen if I take part in this research study?"* while the answer is provided in second person: *"You will be given one dose of the investigational medicine through your vein over a time period of one hour."*
- Write in simple short sentences; avoid abbreviations and acronyms.
- Use a type size that is at least 12 points; balance the layout of text and white space.
- To distinguish the consent form being used, it is useful to create a footer that includes the study title, the consent form version number (because revisions are often made after the initial IRB approval), and IRB approval date. This should be included on every page along with page numbers in a format such as "Page 1 of 3" and "Page 2 of 3."

Subjects Do Not Waive Legal Rights

Investigators should be aware that the purpose of the written consent form is not to provide legal protection for researchers and institutions. *No consent form may include exculpatory language through which the subject or legal representative waives or appears to waive any legal rights or releases or appears to release the investigator, sponsor, the institution, or its agent from liability for negligence.*[12]

How to Assess the Reading Level

There are a number of tools that can be used to assess the reading level of a document. Some word-processing programs have a built-in reading level assessment function. Writers may also use the SMOG (Simple Measure of Gobbledygook) index to assess the reading level of a consent form.[13] The SMOG index estimates the number of years of education needed to understand a given sample of text, which can be typed or copied and pasted into an online panel and a reading level assessment made.

Depending on the applicable regulations or guidelines, the appropriate elements described earlier in this chapter must be included in the consent form. When a trial falls under U.S. regulations, a consent form must include the eight basic elements and include any of the relevant six additional elements. Trials conducted under ICH guidelines require the consent form to include all 20 elements.

In some trials, the sponsor will provide a sample consent form that the investigator can modify to meet the needs of the specific investigative site. In addition to inserting the names of the investigator, hospital or clinic, and names and contact information of persons that can answer subjects' questions, there may be specific wording that is required by the local IRB or the hospital legal department. In other trials, a sample consent form is not provided and it is the responsibility of the investigator's team to create the consent form.

With increasingly complex clinical trials, it can be challenging to write a consent form that satisfies the requirements to provide comprehensive information in a language easily understood by the subject. It may be helpful to refer to your local IRB for informed consent form templates; additionally, there are many online resources on how to write a consent form. Your local IRB can also provide you with information about additional inclusions required by local or state laws. For example, the state of California requires the *Experimental Subject's Bill of Rights* to be attached to the written consent form given to subjects, and the consent form given to the subject must be a photocopy of the actual form signed by the subject.

When a Subject Does Not Speak English

Regulations require that the consent form be in a language understandable to the subject. When the study population includes non–English-speaking participants, a translated consent form should be prepared in the languages needed. When working with non–English-speaking subjects, it will be very important to have access to translators to answer questions that come up during the study, or when specific information needs to be communicated to subjects. The investigative team must feel confident that the subject truly understands and gives consent to participate in the study and that information can be communicated between the subject and the study team throughout the duration of the trial.

Obtaining Informed Consent

While the written consent form provides documentation of the process, it does not replace the discussion that should occur between a potential study participant and the individual obtaining consent. One important aspect of obtaining informed consent is to allow subjects adequate time to read the consent form, consider the study, ask questions, and consult with family, friends, or other health care providers before making a decision.

Some considerations when discussing the study with a subject are:

- *Have the discussion in a private place*. Subjects may be uncomfortable if they think others may overhear the conversation. When a private room is not available, find a quiet corner rather than sitting in the middle of a busy clinic.
- *Give your full attention to the subject*. Sit down and make eye contact with the subject. Minimize interruptions by telephone calls, pagers, and other staff. Speak directly to the person and allow family members or caregivers the opportunity to participate in the discussion.
- *Do not rush the discussion*. Allow adequate time for the subject to read the consent form and ask questions.
- *Explain all aspects of the study*. In addition to study purpose and procedures, be sure to review subject responsibilities when participating in the trial. Explain any costs that will be borne by the subject, such as parking fees or time away from work.
- *Distinguish the differences between the research activities and alternative treatment if the subject chooses not to participate*. To avoid therapeutic misconception on the part of the subject, state the purpose of the study as research, clearly identify that therapy is not the purpose of the study, and discuss how decisions made during the study are based upon the protocol.
- *Do not overstate the benefits*. When a trial is not expected to provide any direct benefit to subjects, it should be explained that it holds the prospect of benefits to persons in the future or contributions to scientific knowledge.
- *Assess the subject's understanding of the information discussed*. Ask subjects questions or ask them to explain in their own words, the information discussed. For example, the investigator might say, "In your own words, please tell me why we are doing this study," or "If you take part in this study, what are the things that will happen to you?"

Therapeutic Misconception – the belief held by research subjects that the purpose of the research is to provide therapeutic benefit. Therapeutic misconception can be difficult to prevent when the investigator is the subject's personal physician, leading the subject to believe that decisions made while participating in the study will be in the subject's best medical interest. This is different from **therapeutic hope**, which is the belief that participation in the clinical trial will lead to some benefit.

- *Do not try to persuade the subject to consent*. Consent must be voluntary and obtained without undue influence. Subjects may want time to take the consent form home to discuss participation with a family member or friend.

The consent form must be signed by subjects *before* study participation begins. No study procedures should be performed before consent is obtained.

Physician investigators must be aware that because people often hold their physician in high regard and want to act in a manner as to please them, there is potential for unintentional undue influence. When the subject's personal physician is the person who is asking them to participate, some patients will agree only in an effort to please their physician. Care must be taken to make sure that potential subjects know that their relationship with the physician will not be jeopardized by choosing not to participate in the study.

When a Subject Is Unable to Read

When a subject is unable to read the consent form, the consent form can be read aloud, verbatim, to the subject. When this occurs, there must be an impartial witness who listens to the reading of the consent form and subsequent explanation, and who signs the consent form.

Who Can Obtain Consent from Subjects?

The FDA does not require the investigator to personally obtain informed consent from subjects but does hold the investigator responsible for ensuring that informed consent is obtained from all subjects before study participation begins. The investigator can delegate this activity to other members of the study team, including subinvestigators and Clinical Research Coordinators (CRCs), who must not only be able to answer questions regarding the study, but also be able to assess the subject's understanding of the material and information presented. However, the regulations make it clear that the investigator is ultimately responsible for all study activities, including informed consent. The investigator must ensure that all team members assigned to obtain informed consent have appropriate training and knowledge to be able to meet regulatory requirements.

Documenting Informed Consent

The subject documents his or her consent by signing and dating the consent form. The investigator or team member who led the discussion with the subject should also sign and date the form. When the subject

is not capable of giving consent (e.g., a young child or a cognitively impaired person), the legally authorized representative who gives consent should sign and date the consent form. The subject or legally authorized representative should be given a copy of the consent form; the original consent form signed by the subject should be kept in the site study file. Some sites also require a photocopy of the signed consent form to be placed in the medical records.

Consent should be documented in the medical record or notes. When consent is obtained on the same day that study participation begins, the note should reflect the time of day as well as the date, to provide evidence that consent was obtained before initiation of study procedures. The following is an example of a note written in the medical record documenting informed consent.

10 March 2009
Discussed the study Thrombolytics and Acute Myocardial Infarction with Mr. Connor Davis. This study is sponsored by the GoodHeart Pharmaceutical Company and is a research study comparing the investigational drug ClotAway to the marketed drug ClotFree for patients having a second heart attack within one year of their first heart attack. All aspects of the study were discussed including the study purpose, procedures, risks and benefits, and alternative therapies. Mr. Davis read the study consent form (version 2: 16 Jan 2009) and asked questions. After discussing the study with his son, Mr. Davis decided to participate and signed the consent form at 10:30 A.M. today. A photocopy of the signed consent form was given to Mr. Davis. He will receive the first dose of study drug today.
Sharon McAdams, RN
Cardiology Clinical Research Coordinator

Continuing Informed Consent

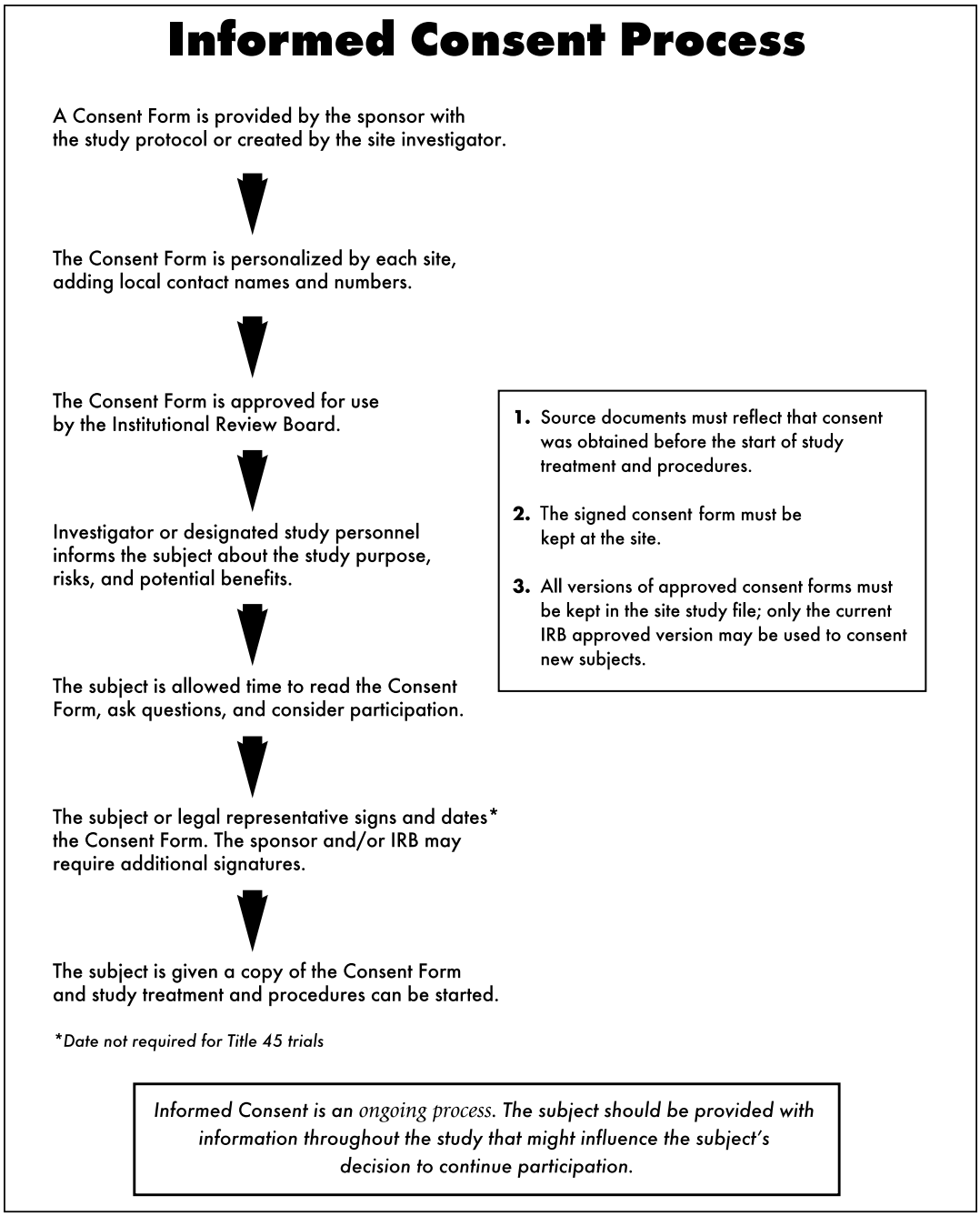
It is important for both the investigator and the study subject to understand that informed consent is an ongoing process that does not end with a signature on a written consent form, but continues through completion of study procedures and follow-up. Study subjects should be informed about the occurrence of new developments that may affect their decision to continue participation in the study.

When the consent form needs to be revised during the study because of protocol amendments or the availability of new safety data, the revised consent form must be reviewed and approved by the

Best Practice – Give Subject a Photocopy of Signed Consent Form

ICH Guideline 4.8.11 states that the subject should receive a copy of the signed and dated consent form; however, 21 CFR 50.27(a) only requires a copy of the consent form to be given to the person signing the form – but not necessarily a photocopy of the *signed* consent form. The HIPAA Privacy Rule (45 CFR 164.508) requires a copy of the signed authorization for use of protected health information to be given to the subject. When this authorization is included in the consent form for the clinical trial, a copy of the signed study consent form should be given to the subject. Therefore, best practice is to always give the subject a copy of the consent form that shows the subject's (or representative's) signature.

Figure 4.3 Informed Consent Process



IRB before use. The revised consent form must be clearly identified with the version number and IRB approval date. While a copy of the original consent form must be kept in the study file, the investigative team must take care to discard or file away other remaining copies of previous versions so that only the current revised consent form is in use.

Some consent form revisions require enrolled subjects who were consented under a previous version to sign the new version as well. For example, if a protocol amendment adds an additional clinic visit for blood tests, this change will affect all enrolled subjects. In this study, the team must inform subjects of the change and ask subjects if they agree to the additional procedure; subjects should sign a revised consent form and be given a photocopy. Both the original and the revised consent forms signed by the subject must be kept in the subject's study file.

In some circumstances, revisions to a consent form do not require previously enrolled subjects to sign a new consent form. For example, if a protocol amendment reduces the number of times that a subject must undergo an ECG during the first month after receiving study drug, there is no need to re-consent the subject who has agreed to the greater number of procedures. For subjects who have already passed the first month after treatment, this protocol change would have no impact on their study procedures and does not represent a safety concern. Therefore, there is no requirement for previously enrolled subjects who have passed the 1-month timepoint to sign a revised consent form.

References

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2 *A Brief History of Military Contributions to Ethical Standards for Research Involving Human Subjects* by Arthur O. Anderson. Scribd (Internet publisher): 8 September 2008

3 http://www.hsl.virginia.edu/historical/medical_history/yellow_fever/mosquitoes.cfm

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6 *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*, Vol. 2, pp. 181–182. Washington, D.C.: U.S. Government Printing Office: 1949

7 http://www.hhs.gov/ohrp/informconsfaq.html#q6

8 21 CFR 50.27(b)(2)

9 The Belmont Report. *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*: 1979
10 http://www.plainlanguage.gov/index.cfm
11 45 CFR 164.508 Privacy of Individually Identifiable Health Information: Uses and disclosures for which an authorization is required
12 21 CFR 50.20 General Requirements for Informed Consent
13 http://www.harrymclaughlin.com/SMOG.htm

5 Institutional Review Boards

In this Chapter

- Types of IRBs
- IRB membership
- IRB review process
- IRB accreditation

"A man is truly ethical only when he obeys the compulsion to help all life which he is able to assist, and shrinks from injuring anything that lives."

Albert Schweitzer (1875–1965), Theologian, musician, philosopher, and physician

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

The World Medical Association Declaration of Helsinki

The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee. (Ethical Principles for Medical Research Involving Human Subjects; last amended: 59th WMA General Assembly, Seoul, October 2008)

The dominant theme in clinical research is the safety and protection of human subjects. A distinction is made between what happens in *clinical practice* – that being treatment – and the goals of *clinical research*, which tests treatments and interventions in order to determine the best treatment practices. The principle that the rights, health, and welfare of human subjects take priority over the needs of clinical research underpins the ethical documents and regulations governing clinical research. These regulations identify a shared responsibility for human subject protection: the study sponsor, the Principal Investigator (PI), and the Institutional Review Board (IRB) work together to provide this protection.

What is an Institutional Review Board?

As provided in the Code of Federal Regulations (CFR) in 21 CFR 56.102(g), the definition of an IRB is "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." A similar but expanded definition is provided by International Conference on Harmonisation (ICH) E6: Guideline for Good Clinical Practice (GCP), Section 1.31, which says that an IRB is "an independent body constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects."

"Institutional Review Board" is a generic term for this group; these committees may be called by other names, including:

- Ethics Committee (EC);
- Research Ethics Board (REB) – a term commonly used in Canada;
- Independent Ethics Committee (IEC) – found in ICH E6 guidelines; and
- Domain Specific Review Boards (DSRBs) – used in Singapore.

Regardless of the group's name, the primary purpose of the IRB is to assure that the rights and welfare of human subjects are protected, both in advance of research implementation and by periodic review once subjects have been enrolled.

Since most research protocols cannot be initiated without IRB approval, the IRB acts as the arbiter of human subject protection. IRBs review research protocols to confirm that:

- The study design ensures equitable subject selection and adequate monitoring of safety and data;
- That there will be proper application of the informed consent process and protection of subject privacy and data confidentiality; and
- Appropriate safeguards are in place for vulnerable subjects.

IRBs may request changes to research-related documents in order to grant approval; IRBs also have the authority to disapprove research protocols. Once approval is given, IRBs are responsible for the continuing review of the research at least annually or at more frequent time intervals that are appropriate to the degree of risk involved for subjects.

Types of IRBs

Investigator familiarity with the type and requirements of an IRB is an important element of a successful application for IRB review and approval. Knowledge of where and to whom to submit documents, deadlines for submission, and IRB meeting frequency all play a part in obtaining timely approval. The frequency with which IRBs meet varies among institutions and IRBs, and typically ranges from weekly to monthly. It may be necessary to submit documents to the IRB a week or more before meetings, giving IRB members adequate time to review the protocol and prepare for the meeting. Investigators will need to

Institutional Review Boards in the Regulations and ICH Guidelines

21 Code of Federal Regulations Part 56, Subpart C – IRB Functions and Operations

21 CFR 56.108	IRB functions and operations
21 CFR 56.109	IRB review of research
21 CFR 56.110	Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research
21 CFR 56.111	Criteria for IRB approval of research
21 CFR 56.112	Review by institution
21 CFR 56.113	Suspension or termination of IRB approval of research
21 CFR 56.114	Cooperative research

45 CFR Part 46 Protection of Human Subjects Subpart A – Federal Policy for the Protection of Human Subjects (Basic DHHS Policy for Protection of Human Research Subjects)

45 CFR 46.107	IRB membership
45 CFR 46.108	IRB functions and operations
45 CFR 46.109	IRB review of research
45 CFR 46.110	Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research
45 CFR 46.111	Criteria for IRB approval of research
45 CFR 46.112	Review by institution
45 CFR 46.113	Suspension or termination of IRB approval of research
45 CFR 46.114	Cooperative research
45 CFR 46.115	IRB records
45 CFR 46.116	General requirements for informed consent
45 CFR 46.117	Documentation of informed consent

ICH E6: Guideline for Good Clinical Practice-Institutional Review Board/Independent Ethics Committee

3.1	Responsibilities
3.2	Composition, Functions, and Operations
3.3	Procedures
3.4	Records

know if their institution has its own IRB or if they should submit clinical trial documents to an independent IRB.

Local IRBs

Local IRBs are affiliated with an institution, such as a hospital, university, medical center, or group of care facilities; thus, local IRBs are geographically close to and knowledgeable about the institutions, investigators, and community of potential subjects participating in the research. In most cases, an investigator who is affiliated with a specific institution must apply for approval from the local IRB associated with that same institution. Some IRBs review all protocols within an institution regardless of the area of study, while other IRBs have been set up to review specific areas of medicine or science. For example, some institutions have established IRBs that review only protocols within a specific domain or area, such as oncology or cardiology. This allows IRB members to bring to bear their expertise in the sub-specialty area, resulting in a more effective and efficient review of submitted protocols. Local IRBs often charge for their services; investigators may want to negotiate with study sponsors to pay the local IRB fees.

Independent IRBs

Not all institutions have IRBs; instead, some may arrange for an "outside" IRB to review research. These outside IRBs, which are not associated with any specific institution, are referred to as independent IRBs, central IRBs, or national IRBs. As the workload for IRBs has increased, so has the time it takes to complete a protocol review. This has led to an increase in the number of independent IRBs, which may be able to offer more efficient services to clinical sites, often with a quick turn-around time for protocol review. Instead of multiple local IRBs reviewing the same research protocol for a multi-site study, one central IRB can review the project for all participating institutions. In this way, the independent IRB may eliminate duplication of effort and reduce the workload of local IRBs. Independent IRBs are commercial enterprises and require payment for their services. Independent IRBs can be used by investigators when there is no local IRB, or when the local IRB cedes its review responsibilities to the central organization. These IRBs review and approve protocols for many investigators at different institutions.

IRB Membership

According to regulations, IRBs must have a minimum of 5 members [as described in 21 CFR 56.107(a) and 45 CFR 46.107(a)] of varying

backgrounds, a recommendation also made in ICH E6 guidelines for Good Clinical Practice [3.2.1(a)]. IRB members must have appropriate qualifications based on education and work experience, so that members can effectively review a wide range of research protocols. IRB members must be individuals:

- of both sexes, when possible;
- who are sufficiently qualified with varying backgrounds, expertise, and experience, as well as racial and ethnic diversity;
- at least one of whom is not employed by or affiliated with the institution, or a part of the immediate family of someone who is employed by or affiliated with the institution;
- one of whose primary concern or work is in a scientific area; and
- one of whose primary concern or work is non-scientific.

The regulations state that every effort should be made to prevent an IRB made up solely of men or of women, and that an IRB may not be made up entirely of members from a single profession.[1]

Scientific versus Non-Scientific Background

Members with a scientific background may include nurses, pharmacists, physicians, and others with training and education in the health care or life sciences fields. Individuals such as clergy, lawyers, and ethicists may be considered non-scientific members. Often the non-scientific member also fulfills the requirement for a member not affiliated with the reviewing institution; for example, a lawyer might be considered both a non-scientist and a member not affiliated with the institution.

Awareness of Community Attitudes

Sensitivity to community attitudes is one of the requirements of an IRB.[2] It is important that some IRB members are familiar with and able to communicate local cultural, religious, and language concerns to the general IRB, which is charged with evaluating whether a research project could place the community at greater risk of harm.

What to Do When an IRB Member Is Involved in the Research Project under Review

IRBs may not permit a member who has a conflicting interest to participate in the initial or continuing review of a project, except to provide information as requested by the IRB.[4] When an IRB member is involved in the research being reviewed – for example, the member is a study investigator – the IRB member must recuse

Community Awareness of a Clinical Trial Involving a Blood Substitute

In 2005 Duke University Medical Center began a clinical trial testing a blood substitute to be administered to people who were critically injured and bleeding due to trauma. Eligible subjects would be in shock due to severe bleeding and therefore unable to give consent to participate in the study. Under FDA regulations, clinical research in emergency settings is allowed using an exception from the informed consent requirement (21 CFR 50.24). To obtain the waiver of documentation of informed consent for the study, investigators held a series of public meetings to educate the public about the study. The proposed study met with approval from members of the community. However, because there was an awareness that not everyone would be willing to participate, provisions were made to allow people the opportunity to opt out of study participation. Those persons who opted out (by writing a letter indicating that they would not wish to participate) were provided a special identification bracelet. The Duke University Health System IRB approved the study based on the regulations for exception from documenting consent and the efforts to educate the public regarding the study.[3]

him or herself from the discussion and review, and abstain from voting. It is acceptable for the member to provide additional information about the research when asked to do so by the IRB committee, but the member should not participate in further discussion or vote. The IRB must meet the minimum qualifications (five or more members; diversity; one scientific and one non-scientific member; etc.) without the participation of the recused IRB member.

Vulnerable Subject Protection

IRBs and investigators should be familiar with the following regulations when conducting research in these vulnerable populations.

Title 21, Part 50, Subpart D Additional Safeguards for Children in Clinical Investigations

Title 45, Part 46, Subpart B Additional Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research

Title 45, Part 46, Subpart C Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Title 45, Part 46, Subpart D Additional Protections for Children Involved as Subjects in Research

Member Who Is Knowledgeable about Vulnerable Subjects

When an IRB regularly reviews research that involves vulnerable subjects, such as children, prisoners, pregnant women, and handicapped or disabled persons, the IRB must have a member who is knowledgeable about issues affecting the specific subject population and the regulations protecting them.[5]

The ICH guideline for Good Clinical Practice defines vulnerable subjects as:

> individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.[6]

By this definition, persons who should be considered as vulnerable subjects include: patients with incurable diseases; persons in nursing homes; unemployed or impoverished persons; patients in emergency situations; ethnic minority groups; homeless persons; nomads; refugees; minors; and persons incapable of giving consent. Examples of individuals in a hierarchical structure requiring protection include students (e.g., medical, pharmacy, dental, and nursing students), subordinate hospital and laboratory personnel, members of the military, and persons in detention. Regulations in Titles 21 and 45 identify children, pregnant women, fetuses and neonates, and prisoners as vulnerable subjects.

Outside Experts

If an IRB believes that review of a research project requires additional expertise outside that of its members, the IRB can invite persons with relevant expertise or competence in special areas to assist in the review process.[7] For example, when reviewing a complex clinical trial in the field of oncology, the IRB might invite an oncologist with experience treating the specific cancer targeted in the study to attend the meeting. These experts can provide the necessary explanation,

clarification, and recommendations for IRB members, but are not allowed to vote with the IRB.

IRB Activities

Although IRBs carry out a number of activities, their primary duty is to review research proposals. When reviewing research, IRBs are responsible for ensuring that investigators adhere to regulatory responsibilities regarding subject safety, and in particular, ensuring that an informed consent process is being implemented. IRBs also have reporting activities that relate to unanticipated problems involving risks to subjects or others. IRBs must be familiar with the local laws pertaining to clinical research, as there may be state or other local requirements in addition to the existing federal regulations. For example, all subjects participating in a clinical study in the state of California must be given a copy of the California *Experimental Subject's Bill of Rights* (see Chapter 3). IRBs must establish written policies and procedures for all IRB activities.

Reviewing Research

IRBs review research proposals and have the authority to approve the research, require modifications for the purpose of approving the research, and disapprove research proposals. IRBs have the authority to place a research study on "administrative hold" when additional information is needed. IRBs can also terminate or suspend previously approved research if there is reason to believe there has been a violation of the rights or welfare of subjects, if there is new information regarding an increased risk to subject safety, or if there is serious or continuing investigator non-compliance with any of the regulations or IRB policies.

Most clinical research requires IRB review and approval before investigators are allowed to begin the research. The IRB must determine whether the study exposes subjects to more than "minimal risk," the threshold that makes IRB approval mandatory before initiating the study. The definition of minimal risk provided in 21 CFR 56.102(i) is "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."

Because this definition of minimal risk can be ambiguous when applied to real-life situations, clarification has been provided by the

IRB Review of a Proposed Clinical Trial

The IRB should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed, and the dates for:

- approval/favorable opinion
- modifications required prior to its approval/ favorable opinion
- disapproval/negative opinion
- termination/suspension of any prior approval/ favorable opinion[8]

Secretary's Advisory Committee on Human Research Protections (SACHRP), an advisory committee to the Office of Human Research Protections (OHRP) in the Department of Health and Human Services (DHHS). For example, in clinical trials that involve children, minimal risk should be interpreted as risks encountered during daily life by normal, average, healthy children living in safe environments. When prisoners are involved as research subjects, the fact that their daily life in prison represents greater situational risk does not equate to a tolerance of greater risk when the subject participates in research. The risk standards for prisoners should be referenced to healthy persons in safe environments, rather than healthy persons in prison.[9]

To determine whether to approve a research study, an IRB must review and evaluate the following aspects:

Study Design: The study design will be reviewed by the IRB to ensure that it is scientifically valid and that the protocol incorporates the appropriate research methods to answer the clinical question.

Evaluation of benefit versus risk of harm: The IRB must be assured that the risks of harm to subjects are reasonable compared with potential benefits; the knowledge gained by conducting the study must be important and unobtainable through other efforts.

Fair and equitable selection of subjects: To determine if subject selection is equitable, the IRB will review the eligibility criteria to determine who will be enrolled – men, women, children, healthy volunteers – and if vulnerable subjects are to be enrolled, the IRB will determine if adequate safeguards are in place to provide protection. When study advertisements or other public announcements will be used to recruit subjects, these materials will be reviewed by the IRB to determine the accuracy of information and absence of undue influence.

Informed consent process: The IRB reviews the informed consent document to determine whether it accurately includes and describes all elements required by the regulations, and whether the language is understandable to the target population. The IRB will review the consent form to ensure that it does not include exculpatory language implying that the subject (or legal representative) waives any rights, or releases the investigator, study sponsor, or institution from liability for negligence. To be sure that regulatory requirements for the informed consent process are met, an explanation of who will obtain informed consent, as well as when and how this will be done, should be provided to the IRB. Information provided to the IRB should describe the steps in the ongoing process of keeping subjects informed throughout the study. When children are prospective subjects, an age-appropriate Assent Form for children should be submitted for IRB review.

Protection of subject privacy and confidentiality of data: Regulations require IRBs to protect the privacy of subjects and maintain confidentiality of the data [21 CFR 56.111(a)(7)] [45 CFR 46.111(a)(7)]. In addition to the requirements in the CFR, another layer of protection has been legislated through the *Health Insurance Portability and Accountability Act (HIPAA).* HIPAA identifies health information that must be protected and requires authorization for use of this personally identifiable data. IRBs must know what processes have been put in place by sponsors and investigators to safeguard the subject's protected health information.

Depending on the nature and complexity of the study, there may be many other aspects that must be considered by an IRB before it grants approval. Most IRBs have developed forms or checklists for investigators listing all the items required for review.

IRB Review

Some of the aspects the IRB considers before approval:

- study design
- benefit versus harm
- selection of subjects
- informed consent process
- protection of subject privacy

Reporting Unanticipated Problems Involving Risks to Subjects or Others

IRBs must set up procedures for reviewing and reporting unanticipated problems involving risks to subjects or others. When an investigator becomes aware of an adverse event or any other incident, experience, or outcome that represents an unanticipated problem, the investigator must report it promptly to the IRB, as described in 45 CFR 46.103(b)(5)(i) and in the regulations for FDA studies [21 CFR 312.66 and 21 CFR 812.150(a)(1)]. Regulations in 21 CFR 56.108(b)(1) and 45 CFR 46.103(b)(4) require IRBs to follow written procedures to ensure prompt reporting of these unanticipated problems. The report to the IRB should contain information identifying the protocol, including the study title, investigator's name, and IRB project number; a detailed description of the adverse event, incident, experience, or outcome; an explanation of why the investigator considers it an unanticipated problem; and a description of any changes to the protocol, consent form, or other corrective actions to be implemented.

Once an IRB receives a report, the committee needs to determine whether the investigator-reported incident, experience, or outcome meets the following three criteria:

- unexpected (in terms of nature, severity, or frequency) based on the research procedures that are described in the protocol-related documents and the characteristics of the subject population being studied; AND
- related or possibly related to a subject's participation in a trial; AND

Examples of Unanticipated Problems Involving Risks to Subjects or Others

Example #1: An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. These data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work. This is an unanticipated problem that must be reported because the incident was a) unexpected (i.e., the investigators did not anticipate the theft); b) related to participation in the research; and c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

Example #2: As a result of a processing error by a pharmacy technician, a subject enrolled in a multi-center clinical trial receives a dose of an experimental agent that is 10 times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation. Nevertheless, this constitutes an unanticipated problem and the dosing error must be reported to the IRB, appropriate institutional officials, and OHRP because the incident was a) unexpected; b) related to participation in the research; and c) placed the subject at a greater risk of physical harm than was previously known or recognized.

- suggests that the research places subjects or others (for example, family members) at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

The IRB may request additional information from the investigator to make this determination and the IRB must report all unanticipated problems to appropriate institution officials. These officials must then report unanticipated problems involving risks to subjects or others to OHRP.

The following guidelines have been provided by OHRP to comply with the regulatory requirement for prompt reporting:

1. Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.
2. Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
3. All unanticipated problems should be reported to appropriate institutional officials, the supporting DHHS agency head or designee, and OHRP within 1 month of the IRB's receipt of the report of the problem from the investigator.

IRBs typically create a form that investigators should use when reporting unanticipated problems at the institution.

Establishing Written Procedures

IRBs are required by the regulations to follow written procedures regarding the review of research protocols. Written procedures should cover all IRB responsibilities, including prompt reporting of unanticipated problems involving risks to subjects or others, serious or continuing investigator noncompliance with regulations, and suspension or termination of IRB approval for a research protocol. IRBs must follow written procedures to review research at convened meetings at which a majority of the IRB members are present, except when expedited review is used.[10] IRBs are free to develop their own written procedures, but must document their meetings and activities in writing.

Types of IRB Review

There are several types of IRB review. Some research protocols require full committee review, while others may meet criteria for expedited review. Once protocol approval has been given, continuing review of the research is required at least annually. Regulations provide for some research to be exempted from IRB review and approval if subjects participating in the research are not exposed to more than minimal risk.

Full Committee Review

Research studies that do not meet the criteria for an expedited review will be reviewed by the full committee at a convened IRB meeting. When documents are submitted to an IRB for review, they are distributed to IRB members to read before the scheduled IRB meeting. At the meeting, IRB members will discuss the submitted documents and research proposal before voting whether to approve the research, request additional information or changes in order to approve the research, or disapprove it. A majority of IRB members must be present for discussion and voting. Approval of a research study requires a simple majority of members present at the meeting.

Waiver of Informed Consent or Exception for Documentation of Informed Consent for Emergency Research

The very nature of emergency research requires full committee review, but the regulations allow an exception to the requirement for documenting informed consent before study enrollment in some of these studies. For example, studies that enroll subjects who have experienced cardiac arrest, a stroke, or severe trauma may fall into this category of exemption. Subjects in life-threatening situations may not be able to give informed consent because of their medical condition; the investigational treatment must be administered before informed consent can be obtained from the subject or legally authorized representative and there is no way to reasonably predict who will be eligible subjects for the study to obtain consent before the event. The research study must be approved by the IRB, but an exception can be made to the requirement for all subjects to give informed consent before study enrollment and treatment. The reasoning for this exception is based on the possibility of direct benefit for subjects who participate and the understanding that there is no way to conduct the study without the exception [21 CFR 50.24 and 45 CFR 46.116(c)].

The IRB must ensure that procedures are in place to inform subjects – or family members or the legal representatives if the subject remains incapacitated – regarding the subject's inclusion in the study. IRBs usually require a document to be given to subjects after study enrollment and treatment. This information must be presented at the earliest opportunity and should include the details of the study and other information normally included in an informed consent document.

Expedited Review

An IRB can perform expedited review of a study if one of the following is true: 1) there is no more than minimal risk to subjects who participate in the research, or 2) there are minor changes to a study that the IRB approved in the previous 12 months. The expedited review can be performed by the IRB chairperson or by an experienced IRB member designated by the chairperson. Expedited review is conducted outside of the regularly convened IRB meetings.[11]

A research protocol can be approved through the expedited review process, but cannot be disapproved by an expedited review. If the person performing the expedited review believes the research should not be approved, the project must go to the full board for review. IRBs must establish a system to notify all IRB members of research that was approved by means of an expedited review; this is often done by notification at the first meeting after the approval is given.

It is not common for an initial review of a protocol to be eligible for expedited review; however, there are some circumstances when this is warranted. Research that may be eligible for initial review and approval using the expedited process includes studies that collect data through non-invasive procedures routinely used in clinical practice. Examples of these non-invasive procedures include ultrasound, echocardiography, electrocardiography, weight measurement, and testing of sensory acuity. Studies that employ a prospective collection of biologic specimens – such as deciduous or permanent teeth extracted through routine care or hair clippings collected in a non-disfiguring manner – may also be eligible for expedited review.

In some circumstances, previously-approved research that is undergoing continuing review may fulfill criteria for expedited review, such as a previously-approved protocol in which enrollment is closed, all subjects have completed study-related interventions, and the research is ongoing only to complete long-term subject follow-up. The categories of studies that may be eligible for initial and continuing expedited review, as well as many examples in each category, can

be found in the guidance document titled *Categories of Research That May be Reviewed by the IRB through an Expedited Review Procedure*, available on the OHRP Web site.[12]

Items That Must be Submitted for IRB Review

Investigators are responsible for submitting study-related items to IRBs for study review and approval. These include:

- a curriculum vitae (CV) for each investigator – the CV must include investigator qualifications, education, training, and work experience;
- the study protocol (refer to Chapter 9 for a description of what should be included in a protocol);
- investigator's brochure;
- informed consent document;
- advertisements that will be used to recruit subjects;
- all study materials that will be provided to subjects, including educational materials and incentives; and
- payment schedule for subjects, when applicable.

Often IRBs will provide an application form or submission checklist unique to the institution and IRB. This form should be completed by the investigator and submitted with the required documents. Investigators must wait until IRB approval is received before starting the study; this includes any advertising or recruitment of subjects.

Exemptions: When IRB Approval Is Not Required

Registries, databases, and specimen banks used to store data and/or specimens for future clinical purposes or quality improvement (i.e., not research) do not require IRB approval.[14] For example, a database used to collect information on diabetes – determining the percentage of diabetic patients who have routine hemoglobin (HgA1c) testing, annual neuropathy exams, annual

Subject Payment and Incentives

Some subjects are paid for participating in clinical research. This payment may be in the form of money, or may take the form of rewards such as free medical care or extra vacation time, and it is sometimes provided as gifts such as pens, notebooks, or bags. IRBs must determine whether these payments are appropriate or if they represent undue inducement, providing offers too attractive or valuable for subjects to turn down. Some IRBs have developed written policies to address the recruitment and payment of subjects and may require investigators to: 1) detail the terms of payment or reward in the consent form; and 2) describe the situations for partial payment (e.g., if a subject drops out before completing all follow-up) or no payment (e.g., subject signs consent form but withdraws consent before any study intervention is performed). The IRB will try to ensure that payment or rewards are equal to the inconvenience or discomfort experienced by trial subjects (e.g., subjects who have no invasive procedures and are required to make two follow-up visits might receive only a modest payment). Some IRBs have developed standard remuneration for subjects on a per-sample basis, or developed a proposal for subjects to receive payment according to time spent – an hourly rate, or a fixed amount based on the duration of the study. The IRB should take into consideration subjects' education and socio-economic status as well as community resources to help determine appropriate levels of payment and reward. The IRB's goal is to ensure that consent is truly informed and completely voluntary, without coercion or undue influence, and that incentives are reasonable and appropriate given the complexities and inconveniences incurred by study participation.[13]

Quality Improvement

Quality improvement (QI) programs are useful in determining how things work, where problems exist, and what can be done to make improvements. Hospitals and institutions often have quality improvement programs to conduct both prospective and retrospective review of health care. These QI programs are exempt from IRB review and approval. IRBs may also have quality improvement programs; these may be to identify and improve their existing processes for research review, approval, and record keeping.

lipid testing, and annual retinopathy screening – would be exempt from IRB approval, since the purpose would be to examine diabetes practices as part of the institution's quality improvement program.

Activities that do not expose subjects to greater than minimal risk may also be exempt from IRB review and approval. According to the definition of minimal risk, an exempt study does not expose subjects to physical, psychological, or social risks beyond that ordinarily encountered in daily life.

Studies in which subjects are required to complete surveys and the information requested does not place the subject at risk may be considered exempt from IRB review. However, a questionnaire that asks subjects about an illegal behavior such as illicit drug use could place subjects at risk for criminal prosecution or loss of employment; therefore, a study using such a questionnaire would pose more than minimal risk and would **not** be exempt from the requirement for IRB approval before use.

The determination of exemption cannot be made by the study investigator. If an investigator believes a research study does not represent greater than minimal risk to subjects, the investigator will need to determine if the study meets the regulatory requirements for exemption from IRB review and approval. To do this the investigator should contact the IRB to learn how these decisions are made within the institution, and by whom – the IRB, or another research board within the institution.

Continuing Review after Initial Study Approval

Routine continuing review of the research provides the IRB with an opportunity to observe the progress of the entire study. IRBs must conduct continuing review of previously-approved protocols at least once a year, and may do so more frequently based on the IRB assessment of the nature of the study, the degree of risk of harm to subjects, and subject vulnerability. The regulations provide IRBs with the minimum requirements for continuing review, allowing IRBs to establish their own rules and methods for conducting this review. IRBs often create their own forms or checklists requesting specific information from investigators. In general, the information that is requested by IRBs includes:

- status of the study (e.g. is the study open and enrolling subjects? Is enrollment closed? Is data analysis ongoing?);
- number of subjects consented, enrolled, active, completed;
- number of subjects withdrawn from the study and reasons why;

- summary of significant protocol deviations and steps taken to prevent future deviations;
- description and outcome of serious adverse events and unanticipated problems involving risks to subjects or others;
- confirmation of the current protocol (and approved amendments) and consent form (with applicable approved revisions);
- current risk-benefit assessment;
- new information since the last IRB review.[15]

IRB review and re-approval of the research study must take place before the study's IRB approval expires. If the initial approval expires before continuing review and approval, new subjects should not be enrolled in the study until continuing IRB approval is granted.

Protocol amendments must be submitted to the IRB for review and approval. The changes required by the amendment cannot be implemented until IRB approval for the amendment is obtained; changes made to a previously-approved consent form must also have IRB approval before the revised document can be used. The exception to this rule is when the protocol change is needed to eliminate an apparent immediate hazard to the safety and well-being of subjects. When a protocol change is based on this need, the change should be implemented immediately, and the IRB must subsequently be notified.

Review of Adverse Events and Unanticipated Problems

IRBs review adverse event reports submitted by investigators as part of their responsibility for the oversight of the safety and welfare of human subjects. When an adverse event report or safety report is received by the IRB, the committee will review the information to determine whether:

- the study protocol and consent document give subjects complete and accurate information regarding potential risks of harm;
- the risk-benefit ratio for the study continues to be reasonable and acceptable; and
- previously enrolled subjects should be informed about new risks identified in safety reports.[16]

IRBs also are responsible for reporting unanticipated problems involving risks to subjects or others to the appropriate offices, including institutional offices, sponsors of research studies, and the OHRP.

Communication between IRBs and Investigators

Investigator Notification of the Outcome of IRB Review

IRBs must notify the investigator in writing regarding the outcome of votes on a research project. If the research is approved, the IRB letter should specify the exact name of the protocol and the date or version number of the protocol as well as the date and/or version number of the consent form that has been approved. Advertisements, subject educational materials, and other documents also require IRB approval before use.

When an IRB does not approve a research project, the IRB letter should specify the reasons for this decision; the investigator may make changes to the research or try in other ways to address the concerns of the IRB and resubmit the revised protocol for review.

Communication During Study

Over the course of a study, there are multiple opportunities for communication between the IRB and the investigator. In addition to communication regarding the submission of a research protocol, the review and its outcome, and continuing review of previously approved research, there are other forms of communication that should occur on a timely basis. The investigator must promptly report all changes in research activity to the IRB, which might include a protocol amendment and subsequent changes in the consent document. The investigator has an obligation to not implement protocol/consent form changes before receiving IRB approval, except when necessary to eliminate an apparent immediate hazard to subjects.[17] The investigator must report potential unanticipated problems involving risks to subjects or others so that the IRB can make appropriate determinations. Serious adverse events should also be reported to the IRB and are often submitted as "safety reports" provided by the study sponsor. Depending on the study, the IRB may ask for additional communication; for example, reporting of all strokes or subject deaths. When a study uses a Data and Safety Monitoring Board (DSMB) to review data and safety at prespecified intervals during the study, the investigator should provide a copy of the DSMB summary to the IRB.

IRB Notification at Study Completion

IRBs are required to follow written procedures that, among other things, ensure "prompt reporting to the IRB of changes in research activity."[18] The completion of a study is considered a change in research activity and must therefore be reported to the IRB by the investigator. To fulfill this regulatory requirement, most IRBs ask investigators to submit a "final report" when all subjects have completed final visits/follow-up and the sponsor has indicated that the study is closed at the site. If the study was conducted under a Federalwide Assurance (which guarantees human subjects protection for studies that receive U.S. federal government funding and support under the regulations in 45 CFR 46), all data analysis at the site must be completed before submitting a final report. IRBs may provide a form for investigators to complete and submit after the study has been completed; this final report typically requests information such as the total number of enrolled, completed, and withdrawn subjects, and a summary of serious adverse events or unanticipated problems not previously reported to the IRB.

Communication between IRBs and Study Sponsors

In general, the line of communication regarding clinical trials is between the site investigator and the IRB. Investigators submit documents directly to the IRB for initial and continuing review. Serious adverse events, safety reports, and progress/final reports are also submitted directly to the IRB by investigators.

However, some FDA regulations require direct communication between IRBs and the trial sponsor. For example, IRBs and sponsors must communicate directly for medical device studies

Some IRB responsibilities for studies of drugs, biologics, and devices are:

1 reviewing, approving/disapproving, or requiring modification of all research activities covered by the regulations;

2 requiring documentation of informed consent in accordance with the regulations, except in the cases when written consent can be waived for some or all subjects because research activities present no more than minimal risk of harm and involve no procedures for which written consent is required outside the research context;

3 providing investigators and institutions with written documentation of approval, disapproval, and/or required modifications of all research activities;

4 reviewing the research at least once a year in accordance with the regulations;

5 ensuring that IRB committee membership consists of at least 5 members:

   a) of both sexes, when possible, and sufficiently qualified with different backgrounds, expertise, experience, and diversity including consideration of race, gender, cultural backgrounds, and sensitivity to community attitudes

   b) at least one of whom is not employed by or part of the immediate family of someone who is employed by or otherwise affiliated with the institution

   c) one whose primary concern or work is in a scientific area

   d) one whose primary concern or work is non-scientific;

6 ensuring that any member who has a conflicting interest in a project reviewed by the IRB will not participate in the initial or continuing review of the project, except to provide information as requested by the IRB.

A full list of responsibilities can be found in 21 CFR 56.107–115, 45 CFR 46.107–115, ICH E6 guidance 3.1–3.4.

as described in 21 CFR 812.2, 812.66, and 812.150(b).[19] These device regulations require IRBs to directly notify the investigator and sponsor when a study presented for approval as a non–significant-risk device is determined by the IRB to be a significant-risk device. Sponsors are required to communicate with all reviewing IRBs information regarding unanticipated adverse device effects, withdrawal of any IRB approval, withdrawal of FDA approval, any requests for an investigator to return, repair, or otherwise dispose of any units of a device, or any other information regarding the device study requested by any reviewing IRB. In addition, sponsors must submit yearly progress reports to all reviewing IRBs (semiannual progress reports for treatment Investigational Device Exemptions) and a final report after termination or completion of the device trial.

When a sponsor and investigators request a waiver of consent for emergency research but the IRB determines that it cannot approve the waiver because the investigation does not meet criteria for exception from informed consent requirements for emergency research, the IRB must notify the sponsor and the investigator(s) promptly in writing [21 CFR 50.24(e), 21 CFR 56.109(e), 21 CFR 312.54(b)]. Sponsors in turn must provide this information in writing to the FDA. This is true for medical device trials as well [21 CFR 812.47(b)].

IRB Records and Reports

IRBs are required to prepare and maintain documentation of their activities. Among other things, regulations require IRBs to maintain:

- copies of all research protocols reviewed, plus approved consent forms, study-related progress reports, and reports of subject injuries;
- detailed minutes of IRB meetings that document IRB member attendance, actions taken by the IRB, the vote on actions with specific for, against, and abstaining counts, the basis for requiring changes in or disapproving research, and a summary of controversial issues and their resolution;
- records of continuing review activities;
- copies of all correspondence between the IRB and investigators;
- a list of IRB members (although this list is not required to be released to study sponsors or investigators); and
- written procedures describing the conduct of initial and continuing review, how it will be decided which projects require review

more often than annually, the process by which investigators should report changes in research activity to the IRB, the process ensuring that these changes will not occur before IRB approval is given, the reporting of unanticipated problems involving risks to subjects or others, and the reporting of serious or ongoing investigator noncompliance with the regulations.

IRBs must keep a copy of all documentation reviewed (protocol, consent form, Investigator's Brochure, subject materials, advertisements, etc.) for at least 3 years after the study is completed at the institution. These records must be available for inspection by authorized FDA representatives.[20]

Accreditation of IRBs

The IRB system of review started out as a volunteer effort to oversee clinical research to ensure the safety and welfare of human subjects. IRB members donated their efforts to review research but were often able to dedicate only a limited amount of time to the process. As the research enterprise has rapidly grown, an almost overwhelming demand has been placed on IRBs. Deficiencies in the system have been identified and a number of IRBs shut down until the process was fixed at each institution/IRB. To improve the system and ensure that necessary checks and balances were in place, individuals and institutions began supporting a movement for the independent evaluation and accreditation of organizations conducting clinical research.

In 1999 the Office for Human Research Protection (OHRP) replaced the Office for Protection from Research Risks, which was responsible for overseeing research at institutions receiving U.S. federal funding. The renamed Office was placed under the auspices of the Secretary of the DHHS in order to place greater emphasis on the importance of human subjects' protection and provide more resources for monitoring and enforcement. Within 6 months of these changes, OHRP initiated a streamlined IRB registration and assurance process.

In 2001, the Association for the Accreditation of Human Research Protection Programs (AAHRPP) was created to promote high quality research through an accreditation process. AAHRPP's goal in accreditation is to "improve the systems that protect the rights and welfare of individuals who participate in research."[21] Accreditation is voluntary and incorporates five domains or areas of responsibility within the human subjects protection program. One of these domains includes IRBs.[22]

As of September 2009 almost 200 organizations (institutions and independent IRBs) have received AAHRPP accreditation. The majority of the organizations are in the United States, but institutions in Singapore, Korea, Canada, and Belgium have also received accreditation. Through this accreditation program and the application of high standards, AAHRPP hopes to raise global standards providing protections to human subjects worldwide.[23]

Registration

In January 2009 the OHRP and FDA simultaneously issued Final Rules requiring IRBs to register via a system maintained by the DHHS. The intention of the new Subpart E of 45 CFR 46 and 21 CFR 56.106 is to create an accurate and comprehensive list of IRBs so as to improve communication between IRBs and government regulators and to facilitate the review of IRBs through inspections. Prior to this, the knowledge of IRBs was limited to information obtained from applications to conduct clinical trials as well as marketing applications. Because some studies are exempt from IND (21 CFR 312) and IDE (21 CFR 812) submission requirements, and many device studies (e.g., non-significant risk devices) are conducted with only IRB approval, these studies were exempt from FDA/OHRP involvement and oversight.[24]

The registration process will require IRBs to supply the following information:

- the name and contact information (address and telephone numbers) for the IRB, the institution operating the IRB, and the IRB chairperson;
- approximate number of all active protocols; and
- a description of the types of products involved in the research studies being conducted under IRB review.

DHHS anticipates that the new registration requirements (effective as of July 2009) will make it easier to convey information to IRBs, and it will support the existing IRB registration system operated by OHRP.

The Final Rule issued by the FDA marks the first time that registration requirements will apply to IRBs for review of FDA-regulated products, including drugs, biologics, and devices involving human subjects.[25]

References

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17 21 CFR 312.66 and 45 CFR 46.103(b)(4)(iii)
18 21 CFR 56.108(a)(3) and 45 CFR 46.103(b)(5)(i)
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6 Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others

In this Chapter

- Why adverse event data are important
- Definition of adverse events
- Unanticipated problems involving risks to subjects or others
- Investigator and sponsor responsibilities when events or problems occur

"Sweet are the uses of adversity,
Which, like the toad, ugly and venomous,
Wears yet a precious jewel in his head;
And this our life exempt from public haunt
Finds tongues in trees, books in the running brooks,
Sermons in stones, and good in every thing."

William Shakespeare (1564–1616), English poet and playwright
From *As You Like It*, Act II Scene 1

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

Adverse Events in the Regulations

Adverse Event (AE) 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 any 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.
(ICH E6 Consolidated Guideline: 1.2)

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.
(21 CFR 312.64)

Investigator Commitment 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.
(Form FDA 1572)

One of the most important responsibilities of the site investigator is the accurate, timely, and complete reporting of adverse events (AEs). The safety of research subjects is best served when investigators and their staff take a systematic approach to collecting and reporting adverse event data. However, investigators sometimes face challenges in identifying events that must be reported.

It is important for investigators to be aware of the difference between AEs in the context of a clinical trial as opposed to events that occur in clinical practice. In clinical trials, the identification and reporting of AEs must meet regulatory requirements; however, this is not the case in clinical practice. Because AEs must be reported according to the definitions provided in the protocol, a given clinical trial may be characterized by the recording and reporting of AEs that in the opinion of the investigator are not of clinical significance. For example: 1) a creatinine measurement of 2.1 mg/dL may not be considered clinically significant by the health care provider, but the protocol requires reporting of creatinine values >2.0 mg/dL; 2) a slight worsening of congestive heart failure may be considered part of the usual disease progression by the clinician, but must be reported as an AE in the setting of a clinical trial.

Inconsistent terminology in the regulations adds to the challenges of reporting AEs. Some regulations provided in the U.S. Code of Federal Regulations (CFR) refer to "adverse events," while others use the term "adverse effect" and "adverse experience." Device regulations use the term "unanticipated adverse device effect" [21 CFR 812.3(s)]. The regulations in 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)(1) require written procedures for reporting to the Institutional Review Board (IRB) "any unanticipated problems involving risks to subjects or others . . ." The glossary in the International Conference on Harmonisation (ICH) E6 guidelines for Good Clinical Practice (GCP) provides definitions for "adverse events," "adverse drug reactions," and "serious adverse events." Reporting requirements are mentioned in ICH, Section 4.11: "all serious adverse events should be reported immediately . . . except those that are designated in the protocol or investigator brochure as not needing reporting immediately."

Why Collect Adverse Event Data?

AEs are collected in clinical trials to:

1 determine the safety profile of a drug, biologic, or device;

2 evaluate the benefits and risks of a product; and

3 provide information for the package insert if the product is approved for marketing.

Safety Profile

The safety profile of a drug, biologic, or device is carefully monitored in clinical trials to determine whether there are any significant concerns that would prevent the product or test article from being used in its intended patient population. The Investigator's Brochure contains all AEs reported in trials of the test article to date, and describes the number of times specific events were reported. Sometimes test articles are found to be effective but have such serious unwanted effects that further studies are discontinued.

Benefits and Risks Evaluation

The U.S. Food and Drug Administration (FDA) recognizes the need for a medical risk-benefit judgment to be made as part of the process of approving a test article for marketing. In this evaluation, the FDA considers whether the benefits of the test article outweigh its known and potential risks, as well as the need to answer remaining questions about its effectiveness.[1] Included in the FDA assessment of the risk-benefit ratio is a careful evaluation of all AEs reported during clinical trials.

Benefit versus Risk:
"Take AZT, for example," said Robert Temple, MD, former director of the Office of Drug Evaluation at the FDA's Center for Drug Evaluation and Research. (AZT, marketed as Retrovir, is used to treat AIDS.) "It has significant toxicity. If you weren't quite sure it had a benefit, it would be hard to describe it as 'safe.' But we know from well-controlled studies that it has a benefit. In the first large clinical study with the drug, there were 19 deaths in patients taking a placebo, but only one death among those on AZT."

Package Insert

Sponsors use AE information to prepare package inserts and user instructions for marketed drugs, biologics, and devices. Package inserts, based on scientific facts gleaned from clinical trials, are written to instruct health care providers in the appropriate use of the product for patients and to inform health care providers and patients of potential side effects. The package insert also serves as a reference by which the FDA can evaluate additional AEs reported after marketing. When postmarketing AEs not listed on the package insert are reported, additional investigations may be required and/or the product may be recalled.

Adverse Events

An AE in a clinical trial is generally defined as any unfavorable change in a subject that may occur during or after administration

of the test article. This change does not have to be caused by the treatment to be described as an AE.

AEs can include:

- physical signs or symptoms;
- abnormal laboratory values;
- changes in vital signs, physical examination, or on an electrocardiogram;
- an increase in the frequency or intensity (worsening) of a condition or illness that was present before study enrollment;
- complications from a surgery or procedure;
- device malfunction or failure;
- device user error;
- psychological harm.

AEs are NOT:

- procedures or surgeries (the medical condition that caused the need for the procedure or surgery is the AE);
- pre-existing events or illnesses that do not worsen during the study period.

Internal and External Adverse Events

In the context of multi-center clinical trials, *internal AEs* are those that occur to subjects at one investigative site. The investigator usually learns about an internal AE directly from the subject, from the subject's health care provider, or from another investigator at the same site. *External AEs* are those events that occur at other sites participating in the study, or that may be events occurring in other studies of the same test article. Site investigators are often not aware of external AEs since they occur to subjects at other institutions. If an external AE or series of events is determined to be unexpected or to represent an increased risk to subjects, the study sponsor notifies all investigators of the event. This may also result in a change to the protocol via a protocol amendment and/or changes to the consent form; these changes must receive IRB approval before implementation.

Serious Adverse Events

A subset of AEs is considered to be serious when events meet any of the six defined criteria, regardless of the relationship of the adverse

event to the test article. A *serious adverse event (SAE)* is defined as any experience that meets *one or more* of the following conditions:

1 results in death;

2 is life-threatening and puts subject at immediate risk of death;

3 results in persistent or significant disability/incapacity;

4 requires or prolongs inpatient hospitalization;

5 results in a congenital anomaly/birth defect;

6 is an important medical event that may *not* lead to death, be life-threatening, or require hospitalization if, based upon appropriate medical judgment, the adverse event jeopardizes the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.[2] (For example, allergic bronchospasm requiring intensive treatment in the 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, would be considered important medical events.)

Unanticipated Problems Involving Risks to Subjects or Others

As noted earlier, the regulations refer to unanticipated problems involving risks to subjects or others, without providing a clear definition. However, the current working definition of "unanticipated problems involving risks to subjects or others" comprises any incident, experience, or outcome that meets *all* of the following criteria:

1 unexpected (in terms of nature, severity, or frequency) based on the research procedures that are described in the protocol-related documents and the characteristics of the subject population being studied, AND

2 related or possibly related to a subject's participation in a trial, AND

3 suggests that the research places subjects or others (for example, family members) at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

The reporting pathway for unanticipated problems involving risks to subjects or others should be provided in the protocol. In general,

Unanticipated Problems Involving Risks to Subjects or Others

All three questions must be answered YES for the event or problem to be considered an unanticipated problem involving risks to subjects or others:

1 Was it unforeseen or unexpected?

2 Is it related or possibly related to study participation?

3 Did it cause harm or lead to a possible increased risk of harm (for subjects or others)?

Principal Investigators (PIs) may be required to report unanticipated problems to the sponsor and/or the trial's Data and Safety Monitoring Board, as well as to the IRB. IRBs must report all unanticipated problems involving risks to subjects or others to appropriate institutional officials who then, in turn, must report unanticipated problems to the Office of Human Research Protections (OHRP). To make a definitive determination, the IRB may request additional information from the investigator. IRBs may provide a form that investigators can use when reporting unanticipated problems at the institution.

The majority of AEs are not unanticipated; rather, they are expected to occur in human subjects based on previous clinical experience and have been previously reported in the Investigator's Brochure or on the package insert. However, a small percentage of AEs are unanticipated and must be reported as such.

The FDA recommends a careful review of an event to determine whether it constitutes an unanticipated problem that must be reported to the IRB. In January 2009, the FDA issued a guidance document to clarify the reporting of unanticipated problems involving risks to subjects or others. The following list of AEs is included in the guidance document in order to identify the specific AEs that should be considered as unanticipated problems that must be reported to the IRB:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an adverse event that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of adverse events represents a signal that the adverse events were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals a higher rate in the drug treatment arm versus a control).
- An adverse event that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in

study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects.

- A serious adverse event that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison).
- Any other adverse event or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.

The FDA recommends that the PI or sponsor include an explanation providing the reason that the event meets criteria for an unanticipated event involving risks to subjects or others.[3]

Investigator Responsibilities

Under federal regulations, investigators have an obligation to report certain AEs that affect subjects participating in a clinical study. Investigators are responsible for collecting and reporting to the sponsor or sponsor-designee all pertinent information about AEs as required in the protocol. The protocol should include a plan for safety monitoring and reporting AEs and/or unanticipated problems. Investigators should be aware of the protocol-specified procedures for communicating this information, as well as local institutional reporting responsibilities to the IRB and others regulatory groups or authorities.

Collecting Adverse Event Data

AEs may be observed by the investigator and other personnel who are responsible for the care of the subject, reported spontaneously by the subject, or reported in reply to open-ended questions. Observations of potential AEs should be made objectively and thoroughly. To avoid bias, questions posed to the subject should occur in a systematic but non-specific way, such as, "Have you had any health problems or have there been any changes in the way you feel since you started the study medication?" Asking questions such as "Have you had any headaches?" is too specific and may be suggestive to the subject.

Investigator Safety Reports

Drugs: 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. [21 CFR 312.64(b)]

Devices: An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150)

Reporting Adverse Event Data

Clinical trials may require a different mindset than clinical practice in regard to reporting AEs. An event that in the non-research setting does not require clinical treatment or is not regarded as significant by the investigator must, in the context of clinical research, be reported if it meets the definitions provided in the study protocol. In many trials, investigators are required to report all events to the sponsor, even if the investigator believes the event to be unrelated to the test article. Complete reporting is necessary because the relationship of an event to a test article is not always apparent at a single site, and what appears to be an isolated event may actually be part of a larger pattern occurring in many subjects at multiple sites.

There are different mechanisms for the investigator to report AEs to the sponsor, depending on the type and seriousness of the event, and the process outlined for the specific study. Some events may be reported to the sponsor by recording them on subject data forms, while others will require expedited reporting to the sponsor electronically, via fax forms, or by telephone. AEs that are both serious *and* unexpected usually need to be reported to both the sponsor and the IRB. To maintain subject confidentiality, AE information should be reported using subject identifiers; names or other personal identifiers should not be reported. SAEs that are ongoing or unresolved at the time of reporting will usually require follow-up reporting to document the eventual outcome or resolution of the event. This could include a complete resolution of the event with no residual effects, but situations such as development of a chronic condition or even death might also occur.

Some studies have different timelines for AE reporting in general, as distinct from reporting of SAEs in particular. For example, reporting of AEs might be required through the end of the last follow-up visit, while SAEs might require reporting until 1 month after the final study drug dose.

The protocol should identify reporting timelines and delineate the events that need to be recorded in case report forms or electronic data files. The following data are usually requested:

- *Event*: The AE should be reported in medical terminology. Depending on the sponsor and the trial, you may be asked to report the event as a diagnosis (asthma) or you may be required to report a sign or symptom (bronchospasm or wheezing).
- *Relationship to test article (causality)*: One of the most important components of AE reporting is determining the cause of the event. The investigator will be asked to evaluate whether the AE was related to or caused by the test article. Typically, the

investigator is asked to indicate this relationship as 1) a reasonable possibility or 2) not a reasonable possibility. Some sponsors may ask the investigator to further categorize this as 1) unrelated, 2) remotely related, 3) possibly related (uncertain as to relationship), 4) probably (likely) related, or 5) definitely related. The investigator may also be requested to provide a supporting rationale for the opinion.

- *Severity/Intensity*: "Mild" indicates the subject was aware of but easily tolerated the event. "Moderate" signifies discomfort sufficient to interfere with normal activities, while "Severe" indicates the subject was incapacitated (unable to perform normal activities). Because the evaluation of intensity is a subjective measure, it is not always required; however, when it is requested, the intensity assessment should reflect the AE at its most severe.
- *Seriousness*: If the event meets one or more of the criteria in the definition of a serious adverse event, the event should be classified as serious.

Severity versus Seriousness

The distinction between the *severity* of an event versus the *seriousness* of an event is an important distinction. While severity is based on the intensity of the event, seriousness is based upon the event outcome in terms of whether it poses a threat to the subject's life or functioning. An event can be severe in intensity yet not be classified as serious. For example, vomiting that persists for several hours might be of severe intensity but not constitute an SAE, because while unpleasant, it does not threaten the subject's life or permanent functioning. On the other hand, an event of mild or moderate intensity, such as a stroke resulting in a limited degree of disability would be classified as an SAE, since it meets one or more of the criteria (i.e., significant disability and requires or prolongs hospitalization).

In addition to the items above, the investigator may be required to record pertinent data about the onset and resolution of the event, treatment provided in response to the event, and action taken with regard to study treatment for the subject.

Relationship to Study Participation

Definitely related: The event was clearly caused by study participation and an alternative cause is unlikely.

Probably related: There is a reasonable possibility of study participation causing the event; there is a timely relationship to study procedures and the AE follows a known pattern of response. There is potential for an alternative cause.

Possibly related: The event might have been caused by study participation. The event may follow no known pattern of response and an alternative cause seems more likely.

Unrelated: The cause is known and the event is not related in any way to study participation.[4]

Expedited Reporting of Adverse Events

The protocol should identify specific AEs that the investigator is required to report to the sponsor in an expedited manner. These events, which are determined through discussions between the sponsor and the FDA during the Investigational New Drug Application process, often include SAEs that are unexpected and judged to be

Figure 6.1 Sample Adverse Event Page

Adverse Events

■ Record all adverse events that occurred during the study period.

■ Report serious adverse events in the same terminology as that reported on the Serious Adverse Event Report Form.

HEAT
Hypothetical Example of A Trial

Adverse Events

Adverse Event	Onset Date and Time	End Date and Time	Most Extreme Intensity	Study Drug Discontinued Because of This Event?	Outcome	Relationship to Study Drug	Was this an SAE?
1	[redacted] day / month / year [redacted] 00:00 to 23:59	[redacted] day / month / year [redacted] 00:00 to 23:59 OR ☐ Ongoing	☐ Mild ☑ Moderate ☐ Severe	☐ Permanently ☐ Temporarily ☑ No	☑ Resolved—no sequelae ☐ Resolved—withs equelae ☐ Unresolved ☐ Death	☐ Unrelated ☐ Remote ☑ Possible ☐ Probable	☑ Yes ☐ No
2	__ __ / __ __ __ / __ __ __ __ day / month / year __ __ : __ __ 00:00 to 23:59	__ __ / __ __ __ / __ __ __ __ day / month / year __ __ : __ __ 00:00 to 23:59 OR ☐ Ongoing	☐ Mild ☐ Moderate ☐ Severe	☐ Permanently ☐ Temporarily ☐ No	☐ Resolved—no sequelae ☐ Resolved—with sequelae ☐ Unresolved ☐ Death	☐ Unrelated ☐ Remote ☐ Possible ☐ Probable	☐ Yes ☐ No
3	__ __ / __ __ __ / __ __ __ __ day / month / year __ __ : __ __ 00:00 to 23:59	__ __ / __ __ __ / __ __ __ __ day / month / year __ __ : __ __ 00:00 to 23:59 OR ☐ Ongoing	☐ Mild ☐ Moderate ☐ Severe	☐ Permanently ☐ Temporarily ☐ No	☐ Resolved—no sequelae ☐ Resolved—with sequelae ☐ Unresolved ☐ Death	☐ Unrelated ☐ Remote ☐ Possible ☐ Probable	☐ Yes ☐ No
4	__ __ / __ __ __ / __ __ __ __ day / month / year __ __ : __ __ 00:00 to 23:59	__ __ / __ __ __ / __ __ __ __ day / month / year __ __ : __ __ 00:00 to 23:59 OR ☐ Ongoing	☐ Mild ☐ Moderate ☐ Severe	☐ Permanently ☐ Temporarily ☐ No	☐ Resolved—no sequelae ☐ Resolved—with sequelae ☐ Unresolved ☐ Death	☐ Unrelated ☐ Remote ☐ Possible ☐ Probable	☐ Yes ☐ No
5	__ __ / __ __ __ / __ __ __ __ day / month / year __ __ : __ __ 00:00 to 23:59	__ __ / __ __ __ / __ __ __ __ day / month / year __ __ : __ __ 00:00 to 23:59 OR ☐ Ongoing	☐ Mild ☐ Moderate ☐ Severe	☐ Permanently ☐ Temporarily ☐ No	☐ Resolved—no sequelae ☐ Resolved—with sequelae ☐ Unresolved ☐ Death	☐ Unrelated ☐ Remote ☐ Possible ☐ Probable	☐ Yes ☐ No

related to the study treatment. The sponsor or designated group responsible for drug safety in the trial will outline a process for the expedited reporting of such events. Events requiring expedited reporting are typically reported on a separate SAE Report Form (or some other similar name), on which the investigator provides specific information about the event. This form often includes a narrative description of the event, as well as relevant medical history, laboratory results, diagnostic tests, concomitant medications, treatment, and the outcome of the event.

The SAE Report Form used for expedited reporting is typically faxed to the sponsor safety group; alternatively, the data are entered directly into an electronic SAE database, usually within 24 hours of the investigator learning of the event. A phone call may also be required for reporting certain events, such as those leading to death.

AEs that require expedited reporting are also recorded in the case report form or other applicable data forms. Special care should be taken to record the event with the same terminology and supporting data as were reported on the SAE Report Form, unless over time additional or corrected information has been gathered.

Reporting Unanticipated Problems Involving Risks to Subjects or Others

Regulations require investigators to report promptly to their IRBs information regarding an AE or any other incident, experience, or outcome that represents an unanticipated problem involving risks to subjects or others.[5] However, recent changes in the conduct of clinical trials, including an increased number of multi-center trials and international trials, have resulted in a more complex reporting pathway for unanticipated problems. In particular, the practice of investigators reporting individual unanalyzed events to IRBs – often with limited information and no explanation of how the event represents an unanticipated problem – has led to the submission of large numbers of uninformative reports to IRBs.[6]

The January 2009 FDA guidance acknowledges that since an investigator may be aware of only those events occurring at his or her own site, the sponsor, who receives information on events occurring at all of the investigative sites, may be in a better position to assess whether an event is both *unanticipated* and a *problem* for the study. Investigators participating in multi-center trials may rely on the sponsor to make an assessment and provide the IRB with a report prepared by the sponsor.[7] The report to the IRB should include

Figure 6.2 Sample Serious Adverse Event Form

HEAT
Hypothetical Example of A Trial

Serious Adverse Event Report Form

☑ Initial Report ☐ Follow-up Report

Study Number: 0 0 1 - 1 0 0 Subject Initials: X Y Z Site Number: 1 2 3

Subject Information

Sex: ☐ Male ☑ Female

Date of birth: 09 / MAR / 1946 (day / month / year)

Study Drug Administration

Date and time study drug infusion started: 15 / JAN / 2009 (day / month / year) 10:15 (00:00 to 23:59)

Date and time study drug infusion stopped: 15 / JAN / 2009 (day / month / year) 11:45 (00:00 to 23:59)

Total dose administered: 95 mg

Event Description

■ Record in concise medical terminology

■ Record as a diagnosis rather than symptoms if possible

Event: Bleeding from stomach ulcer

Onset: 15 / JAN / 2009 (day / month / year) 19:40 (00:00 to 23:59)

Outcome:
☑ Resolved – no sequelae – date: 15 / JAN / 2009 (day / month / year) 23:20 (00:00 to 23:59)
☐ Resolved – with sequelae – date: ___ / ___ / ___ (day / month / year) ___ : ___ (00:00 to 23:59)
☐ Unresolved
☐ Death: ___ / ___ / ___ (day / month / year) ___ : ___ (00:00 to 23:59)

Event Description:
Subject vomited large amount of bloody emesis. Gastroscopy done and multiple ulcerated areas seen. Hemoglobin 8.3, Hematocrit 19.6. Hypotension to 82/56. 2 units PRBC given. Started on antacid therapy.

Seriousness	Relationship to Study Drug	Action taken due to AE
☐ Fatal	☐ Unrelated	☐ None
☐ Life-threatening	☐ Remote	☐ Study drug interrupted
☐ Severely or permanently disabling	☑ Possible	☐ Study drug reduced
☑ Prolonged hospitalization	☐ Probable	☐ Study drug discontinued
☐ Required hospitalization		☑ Other medication
☐ Congenital anomaly		☑ Procedure
☐ Other important medical event		☑ Blood transfusion
		☐ Other: _____

Investigator

Investigator name: Ina B. Goode, MD

Person completing form: Mark Philin Date: 16 / JAN / 2009 (day / month / year)

Phone: 123-4567 Fax: 123-4567

Fax this form to the Safety Desk at 321-123-4567 within 24 hours of learning of event.

information identifying the protocol, the study title, investigator's name, and IRB project number. The sponsor's submission of the report to the IRB will satisfy the investigator's regulatory obligation for unanticipated problem reporting. Whether submitted by the sponsor or the investigator, the report should include a detailed description of the AE, incident, experience, or outcome; an explanation of why the investigator considers it an unanticipated problem; and a description of any changes to the protocol, consent form, or other corrective actions to be implemented.

Investigator Reporting of Unanticipated Problems

Investigators are required to report promptly "to the IRB . . . all unanticipated problems involving risks to human subjects or others," including adverse events that could be considered unanticipated problems. [21 CFR 56.108(b)(1), 21 CFR 312.53(c)(1)(vii), and 21 CFR 312.66]

Reporting Unanticipated Adverse Device Effects

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."[8] Unanticipated adverse device effects must be reported by investigators to the sponsor and the reviewing IRB by submitting a report as soon as possible, but no later than 10 working days after the investigator learns of the event.[9]

IRB Responsibilities

After the initial review and approval of a clinical trial, an IRB must conduct continuing review of the study. The primary purpose of both the initial and continuing review is to fulfill the IRB's responsibility "to assure the protection of the rights and welfare of the human subjects." To accomplish this, an IRB must have information concerning unanticipated problems involving risk to human subjects in the study, including AEs that are considered unanticipated problems.[10]

Review and Reporting of Serious Adverse Events

IRBs are responsible for ensuring that studies do not expose subjects to unexpected serious harm, and that the risk-benefit ratio of the study falls within an acceptable range. In order to make this assessment, IRBs must receive information regarding serious SAEs

occurring among subjects participating in a clinical trial. When evaluating an AE report, the IRB will consider:

- The *seriousness* of the adverse event
- The *relationship* of the event to participation in the study
- Whether or not the event was *expected*
- Whether *current or future subjects* need to be informed either by a change in the protocol and consent document or by other written or verbal communication.

Review and Reporting of Unanticipated Problems

IRBs must set up procedures for reviewing and reporting unanticipated problems, including determining whether the investigator-reported incident, experience, or outcome meets reporting criteria, and may request additional information from the investigator to make such a determination. The IRB must then report all unanticipated problems to appropriate institutional officials, who in turn must report the issues to OHRP. The following guidelines have been provided by OHRP to comply with the regulatory requirement for prompt reporting:

1. Unanticipated problems that are SAEs should be reported to the IRB within 1 week of the investigator becoming aware of the event.
2. Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
3. All unanticipated problems should be reported to appropriate institutional officials, the supporting DHHS (Department of Health and Human Services) agency head or designee, and OHRP within 1 month of the IRB's receipt of the report of the problem from the investigator.

IRBs typically create a form that investigators should use when reporting unanticipated problems at the institution.

Sponsor Responsibilities

Sponsors are responsible for both expedited and routine reporting of AEs to the FDA. Reporting then continues even after the test article has been approved for marketing.

Expedited Reporting in Drug Trials

The sponsor is required to report to the FDA in an expedited manner all AEs that are 1) serious, 2) unexpected (i.e., not listed in the Investigator's Brochure), and 3) related to study treatment. The sponsor must report these events in writing to the FDA within 15 calendar days of first knowledge of the event.

When an event is also fatal or life-threatening in addition to being serious, unexpected, and study-treatment related, the sponsor must report it to the FDA by telephone (or fax) within 7 calendar days, followed by a written report within 8 additional calendar days.

In order to meet these regulatory requirements of reporting adverse events to the FDA within the appropriate timeframes, the designated drug safety group will review the SAE Report Form submitted by the site and contact the investigator when additional or supporting data are needed. Follow-up information may be requested for ongoing AEs.

IND Safety Reports

When an AE requires expedited reporting to the FDA, the sponsor generates and submits an IND Safety Report, which includes (but is not limited to):

- A summary of the event
- For an open-label trial, the treatment arm the subject received
- Analysis of similar events that have occurred in this or other trials, both past and present
- Comments on the occurrence of the same AE with similar therapeutic agents in the same patient population.

For example, in a trial studying the use of r-PA (a thrombolytic drug) in subjects with acute myocardial infarction, the report may include the incidences of a particular AE that was observed in other trials of r-PA in similar patient populations

The site will be provided with a modified version of the IND Safety Report that supplies the above information to the sites but without the mandatory FDA/regulatory forms. This report may be referred to as an "Investigator Alert Letter" or "Safety Letter;" when the report is submitted after drug approval and marketing it may be called an "Alert Report."

The site investigator must submit the IND Safety Report to the site IRB. In some cases, after reviewing the IND Safety Report, the IRB may ask that the informed consent form be changed to reflect the new safety information. The sponsor will also update the Investigator's Brochure to reflect the additional event data.

Sponsor Responsibilities in Investigational New Drug (IND) Trials

Sponsors are specifically required to notify all participating investigators (and the FDA) in a written IND safety report of " any adverse experience associated with the use of the drug that is both serious and unexpected" and "any finding from tests in laboratory animals that suggests a significant risk for human subjects" [21 CFR 312.32(c)(1)(i)(A),(B)]. More generally, sponsors are required to "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." [21 CFR 312.55 (b)][11]

Figure 6.3 Sample IND Safety Report

IND Safety Report

To: All HEAT Investigators

From: HEAT Sponsor

Re: Protocol # 2468-00 - HEAT Hypothetical Example of A Trial

Date: February 22, 2009

To assure that all investigators are kept current on safety issues and to comply with all applicable FDA regulations, the following summary of a serious adverse event is being sent to all investigators in the HEAT trial. Although the serious adverse event did not occur in a subject randomized to the investigational study agent, all participating investigators must forward a copy of this report to their IRB/ethical review board. This report should also be filed in your HEAT regulatory binder. Please contact me if you have any questions or require additional information.

Serious Adverse Event Summary

STP is a 76 year old male randomized into the HEAT study on January 29, 2009. The study number assigned was 013-346 and the subject was randomized to placebo. STP has a history of smoking, atrial fibrillation and no history of neurologic events.

Study product (placebo) was administered intravenously per protocol on January 30, 2009, over a 2 hour period. Aspirin was concomitantly administered as per protocol, 325mg orally, within 1 hour of randomization and daily thereafter. On February 3, 2009, the subject experienced symptoms of stroke. A CT scan was performed and a small hemorrhagic stroke confirmed.

Action Taken with Study Product

None. Subject was administered placebo and dosing had been completed on January 29, 2009.

Relationship to Study Product

Not likely.

Outcome

Subject's symptoms of slurred speech and mild right hemiparesis have resolved and subject was discharged to home on February 15, 2009. No further follow-up is required.

Expedited Reporting in Device Trials

Sponsors must immediately conduct an evaluation of an unanticipated adverse device effect and must report the results to the FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect.[12] The IDE regulations, therefore, require sponsors to submit reports to IRBs in a

manner consistent with the recommendations for the reporting of unanticipated problems under IND regulations.

Routine Reporting by Sponsors

In addition to having reported applicable events in an expedited manner, the sponsor must provide the FDA with a semi-annual report that lists study discontinuations due to AEs, all deaths, and all SAEs. Once a New Drug Application is approved, the sponsor is required to submit post-marketing AE data reports on a quarterly basis for the first 3 years after approval, and on an annual basis thereafter.

References

1 21 CFR 312.84(a)
2 Modified from the definition of serious adverse drug experience in FDA regulations 21 CFR 312.32(a)
3 http://www.fda.gov/cder/guidance/OC2008150fnl.htm
4 http://www.research.ucsf.edu/chr/Guide/Adverse_Events_Guidelines.asp#6
5 21 CFR 56.108(b)(1) and 45 CFR 46.103(b)(5)
6 http://www.fda.gov/cder/guidance/OC2008150fnl.htm
7 Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs. January 2009
8 21 CFR 812.3(s)
9 21 CFR 812.150(a)(1)
10 http://www.fda.gov/cder/guidance/OC2008150fnl.htm
11 http://www.fda.gov/cder/guidance/OC2008150fnl.htm
12 21 CFR 812.46(b), §812.150(b)(1)

7 Monitoring, Audits, and Inspections

In this Chapter

- Types of monitoring visits, and what happens at each
- Making your monitoring visit go smoothly
- Audits and inspections by sponsors and the FDA

"Alone we can do so little; together we can do so much."

Helen Keller (1880–1968), Blind & deaf American educator

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

Scientific integrity is the cornerstone of all research. Investigators and sponsors must function with honesty and maintain high ethical standards when conducting clinical trials. As a means to ensure such scientific integrity, regulations hold study sponsors responsible for proper monitoring.[1] On-site *monitoring visits*, performed by persons known as *monitors*, are conducted to oversee the progress of the trial at the investigative site, verify that subjects are giving informed consent, and ensure that the investigator and Institutional Review Board (IRB) meet their regulatory responsibilities. Monitors may also check to ensure that the sponsor's standard operating procedures (SOPs) for investigative sites are being followed. The monitoring responsibilities listed in the International Conference on Harmonisation (ICH) E6 guidelines for Good Clinical Practice (GCP), section 5.18, require sponsors to verify that: a) the rights and well-being of human subjects are protected; b) the reported clinical trial data are accurate, complete, and verifiable from source documents; and c) the conduct of the trial is in compliance with the currently approved protocol and amendments, with GCP, and with applicable regulatory requirements.

In addition to monitoring research sites, sponsors (or the sponsor's designee) may also conduct *site audits* to ensure that study processes and procedures are properly documented and to review subject data and study records to ensure consistency – in a sense to "monitor" the monitor, the site investigator, and the IRB.

Site inspections, usually conducted at only a sample of sites, are performed by the U.S. Food and Drug Administration (FDA) and other regulatory authorities to oversee the sponsor, monitor, investigator, and IRB, and determine whether all groups have met their regulatory responsibilities. Site inspections may include a review of study records, subject data, and processes used to ensure proper evidence and documentation of study procedures, as well as confirmation that standards for good clinical practice were met.

Not all trials are sponsored studies, or performed with the intent to apply for product registration; therefore, not all trials are subject to external monitoring. Many institutions have established internal procedures for monitoring studies as part of their own quality assurance programs. These may include a system to monitor investigator-initiated studies, as well a system to perform quality control – to review the work of particular employees rather than specific studies.[2]

Regulatory Requirement for Monitoring

Sponsors are responsible for ensuring proper monitoring of the investigation and ensuring that the investigation is conducted in accordance with the general investigational plan and protocols contained in the Investigational New Drug (IND) application (21 CFR 312.50) or Investigational Device Exemption (IDE) application (21 CFR 812.40).

A sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation. 21 CFR 312.53(d) (drugs and biologics) and 21 CFR 812.43(d) (devices)

Monitoring Plan

The person designated to oversee the progress of a clinical trial at investigative sites is known as the monitor. Depending on the study organization, the monitor may be affiliated with the sponsor, an Academic Research Organization (ARO), or a Contract Research Organization (CRO), and often has the job title of Clinical Research Associate (CRA). The CRA travels to the study site to meet with the Principal Investigator (PI) and the Clinical Research Coordinator (CRC). CRAs may be located at the sponsor or ARO/CRO headquarters, or may be regionally located to minimize travel time and expense.

At the beginning of a study, the sponsor determines how monitoring will be performed and who will be responsible for monitoring the trial (sponsor CRAs, or CRAs from an ARO or CRO). The monitoring plan is determined based on factors such as the level of sponsor comfort with the sites and monitoring group, the phase of the trial, and the cost of monitoring. Some pharmaceutical companies conducting small to mid-size trials are comfortable only with monitoring 100% of the variables on data forms for all subjects enrolled. Early-phase trials usually require 100% monitoring of data unless the investigational product is well known and has an established safety profile, for example, if previously studied for another indication or in a different subject population.

Monitoring plans employed for large, later-phase trials can vary greatly. Here are a few examples of possible monitoring plans that may be used in these trials:

- The first subject at each site will have all data verified against source documents, followed by 25% of the remaining subjects at each site, plus all serious adverse events (SAEs).
- The first subject at each site will have 100% of the data compared to source documents; the remaining percentage to undergo source document verification will be determined based on cost and experience with the sites.
- Designated (critical) data variables related to safety and efficacy for all subjects will be compared to source documents.

Other options for monitoring strategies are provided on the following page in response to question 4.

The monitoring plan should be included in the study protocol and should provide answers to the following questions:

1 *Will a pre-study visit or initiation visit be required?* When a site and an investigator are known to the sponsor, a *pre-study visit* may not be required. Some trials offer an Investigator Meeting

that brings together investigators from many sites, as a substitute for an *initiation visit*.

2 *How frequently will monitoring visits to each site be conducted?* The frequency of monitoring visits will depend on the number of subjects enrolled, the number of sites involved, the rate of enrollment, and the amount of source document verification to be performed. Other factors that may affect the frequency of visits as the study progresses are the site's performance and enrollment rate, turnover of site study staff, and problems or concerns related to protocol adherence or subject safety issues. Some of these factors – in particular, the percentage of subject data to be monitored – may be discussed and negotiated with the FDA before the trial begins.

3 *What are the responsibilities of the monitors?* Monitors' activities vary from one trial to another. In some trials, the monitor serves as a liaison between the sponsor and the investigative site and is the contact person for all questions, ranging from regulatory documents to specific clinical questions about the study. In other trials, the monitor may have only on-site data verification responsibilities, while other personnel at the sponsor or coordinating center are responsible for answering trial-related questions. Monitors often provide new or inexperienced site personnel with study-specific information and training.

4 *How much source document verification will be performed? What percentage of subject data forms will be reviewed and compared against source documents at the site?* The amount of on-site source document verification will be based on the type of trial and the phase of the study, among other factors. Some options for source document verification are:

- a review of all data variables in the case report forms (CRFs) for all enrolled subjects;
- a review of all data for a percentage (e.g., 5%) of subjects enrolled;
- a review of only specified variables for all enrolled subjects (e.g., all study endpoint data); and
- submission of source documents for data review by the sponsor/ARO/CRO (where data will be entered and reviewed).

Source Data and Source Document Verification

Source data includes all information in original records of original findings, observations, or other clinical trial activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents, which are the records where data are first recorded. Source documents include hospital records, clinic and office charts, laboratory reports, pharmacy dispensing records, recorded data from automated instruments, and reports of the findings of procedures and tests such as x-rays, scans, and surgical operations.[3]

Patient–reported outcomes (PRO) are also considered to be source data. PRO are self-administered assessments and include diaries and questionnaires that require subjects to respond to questions regarding symptoms, functioning, and quality of life. PRO may be collected on paper forms or via electronic submission.

The process of comparing data recorded in subject data forms or electronic files to source data for the purpose of confirming, or verifying, the accuracy and completeness of reported data, is called *source document verification*.

On-Site Monitoring

The CRA has many monitoring responsibilities. ICH E6: Section 5.18.4 lists 17 activities for monitors to carry out; most are easiest to

accomplish when the CRA is at the investigative site. In general, the CRA oversees the site to ensure that the study is conducted in compliance with regulations and GCP guidelines, and that:

1 the study is conducted according to the protocol and applicable amendments;
2 resources at the investigative site are adequate to conduct the trial;
3 required data are collected and recorded accurately, as compared with source documents;
4 investigational product is properly stored and dispensed;
5 informed consent is obtained *before* subjects begin study participation and a plan is in place for continued informed consent throughout the study;
6 enrolled subjects meet eligibility criteria;
7 the site study file is complete and up-to-date, including all reports, notifications, applications, and submissions; and
8 all adverse events (AEs) and unanticipated problems involving risks to subjects or others are appropriately reported.

Types of On-Site Monitoring Visits

Monitoring visits can be divided into four basic types, depending on their timing and the activities performed. These are generally referred to as *pre-study visits*, *initiation visits*, *periodic monitoring visits*, and *close-out visits*. Not all types of visits will be conducted in every study. For example, a pre-study visit may not be required when a study site is well known to the sponsor; initiation visits may be replaced by an Investigator Meeting attended by the PI and CRC; and close-out visits are sometimes conducted by telephone and supported by electronic submission of information.

Pre-Study Visit

A pre-study visit takes place after a potential PI indicates interest in a specific clinical trial. The purpose of this visit is to determine the site's ability to conduct the study. Before the visit, the PI should review the protocol and Investigator's Brochure and sign the Confidentiality Agreement.

During the visit, the CRA will meet with the PI and CRC to verify that they have adequate time to devote to the study, have access to the appropriate subject population, and are not involved with competing clinical trials. The CRA will tour the facility to evaluate

its adequacy and determine the availability of protocol-required equipment. The CRA will also evaluate the facility's suitability for subject enrollment and follow-up, investigational product storage, and data form storage. Other study-specific requirements, such as access to an ECG laboratory or the facility where study-required scans will be performed, will be evaluated as well.

Topics for the Pre-Study Visit

During the pre-study visit, the monitor will discuss the following:

- PI responsibilities and qualifications (summarized in the investigator's CV);
- qualifications of the CRC and other site personnel;
- study objectives, protocol-required procedures, eligibility criteria, and subject recruitment;
- IRB and informed consent requirements;
- AE reporting, source documentation, and record retention;
- space requirements, availability of a secure area for storing investigational drugs, biologics, or devices; availability of required equipment.

In some cases, such as when the investigative site is already known to the sponsor/CRA, the sponsor may allow a pre-study evaluation to be performed over the telephone instead of on-site. When this approach is used, an in-person evaluation of personnel and facilities must be done at the first visit to the site after the study begins.

Because the pre-study visit is meant simply to assess the feasibility of conducting the study at the site and determine whether the site can manage protocol-specific requirements, this visit does not itself obligate the PI or the sponsor to work together on the trial.

Initiation Visit

Once the PI agrees to participate in the study and signs the contract with the sponsor, regulatory documents are accepted by the sponsor, the protocol and consent form are approved by the IRB, and clinical supplies are shipped to the site, a study *initiation visit* may be conducted. This visit verifies that the investigator and other site study personnel understand the investigator's obligations (21 CFR 312 Subpart D for drugs and biologics or 21 CFR 812 Subpart E for devices), the protocol, and the investigational product being studied.

Since there may be some overlap in the topics discussed at the pre-study visit and the initiation visit, the two visits are sometimes combined. Ideally, the initiation visit is scheduled soon after the

arrival of study supplies and just before enrollment begins. In some cases, attendance at a group Investigator Meeting replaces the requirement for an initiation visit. In other cases, the sponsor may require an on-site initiation visit in addition to attendance at the Investigator Meeting.

During the *initiation visit*, the CRA meets with the PI, subinvestigators (if applicable), the CRC, and other personnel related to the study, such as pharmacy and laboratory staff.

Topics for the Initiation Visit

Some of the topics reviewed at the pre-study visit may be discussed at the initiation visit, but in greater depth. These may include:

- study overview, including eligibility criteria, procedures, and access to a suitable subject population;
- review of regulations and GCP guidelines, including informed consent requirements, IRB obligations, AE reporting, and investigational product accountability;
- review of data forms and data recording;
- review of regulatory documents and study file organization.

If a pre-study visit was not conducted, the CRA will take time during the initiation visit to verify that study staff have adequate resources and time to dedicate to the study, and confirm that the facility is adequate to conduct the study – e.g., the laboratory is properly certified and suitable space is available for drug, device, or related equipment storage.

Periodic Monitoring Visits

After one or more subjects are enrolled in the study, a monitoring visit may be scheduled to evaluate how the study is being conducted and to perform source document verification. While there is only one pre-study visit or initiation visit conducted per site, there may be numerous *periodic monitoring visit*s conducted at each site throughout the trial. The number of visits will be determined by several factors outlined in the monitoring plan, including the number of subjects enrolled and the percentage of records that require on-site review and source document verification.

Topics for Periodic Monitoring Visits

Regardless of how often a CRA visits a site or the amount of data reviewed, each *periodic monitoring visit* is designed to ensure that:

- the PI and other trial personnel are fulfilling their obligations as set forth by regulations and GCP guidelines;
- the trial is being conducted according to the protocol and any deviations are appropriately documented;
- enrolled subjects meet study eligibility criteria;
- informed consent was properly obtained before study participation;
- subject data are accurate and complete when compared with source documents;
- investigational product accountability procedures are being followed;
- SAEs and unanticipated problems involving risks to subjects or others are documented and reported appropriately;
- the PI and CRC are providing the IRB with timely reporting of study progress and safety; and
- proper filing and storage of study documents is maintained.

Because the CRA has observed how the study is conducted at various other institutions, he or she may also offer helpful suggestions to facilitate enrollment and protocol adherence. The CRA may be able to share worksheets, educational tools, and additional items created by other investigators and CRCs that have improved protocol and subject compliance or ensured documentation of protocol-designated data points. The CRA will also inform the PI and CRC about any new information regarding the study.

When contacting the CRC to schedule a periodic monitoring visit, the CRA will request that subject data forms and SAEs forms for subjects enrolled since the previous monitoring visit be made available. Signed consent forms and source documents should be available as well for review and source document verification.

Preparing for a Periodic Monitoring Visit

To prepare for a *periodic monitoring visit*, the PI and CRC should confirm that the following activities have been completed in order to ensure a productive monitoring visit for both the CRA and the site study personnel:

- find a quiet place for the CRA to work (e.g., an office, conference room, medical records department) with access to a telephone, fax, and photocopy machine; the CRA may also need Internet access during the visit;
- complete all applicable subject data forms prior to the visit;

- confirm that SAEs have been documented and reported, and are available for review during the visit;
- obtain necessary source documents for study subjects who require source document verification of data. Medical records and transfer records from external medical offices and hospitals may be needed;
- organize study file documents for review;
- confirm that signed consent forms for all enrolled subjects are available;
- schedule an appointment for the CRA to meet with the pharmacist, if requested;
- schedule time for the CRC to meet with the CRA to review all data forms monitored during the visit and to discuss the trial's general progress trial (e.g., enrollment strategies and protocol adherence);
- schedule a meeting between the CRA and the PI to review the findings.

Checking data against source documents, clarifying discrepancies and misinterpretations on data forms, and observing and providing practical ideas for implementation of the protocol at specific sites make periodic monitoring visits an integral aspect of a successful clinical trial. The Periodic Monitoring Visit Checklist on the following page is an example of one that may be used by a CRA when conducting a site monitoring visit.

Close-Out/Study Completion Visits

A *close-out visit* may be the last in a series of routine monitoring visits, or it may be scheduled specifically for this purpose once the study has been completed and all subject data forms have been submitted.

Topics for a Close-Out Visit

During an on-site *close-out visit*, the CRA may:

- discuss timelines and strategies for completing outstanding data and queries;
- oversee the return or destruction of unused test product;
- collect outstanding subject data forms and study forms such as the Site Visit Log and Screening Logs;
- perform a final review of study file documents;

Figure 7.1 Periodic Monitoring Checklist

Periodic Monitoring Visit Checklist

Subject Status

___ Discuss subject recruitment strategies
___ Ensure correct randomization procedures and maintenance of study blind
___ Verify the status of all study subjects
___ Confirm enrolled subject eligibility
___ Check consent forms for proper signatures and dates before study enrollment

Study Supplies, Storage, and Accountability

___ Ensure that adequate study drug/device supplies are available
___ Check expiration of study drug/device
___ Ensure the accuracy of receipt and dispensing records
___ Meet with personnel who dispense study drugs/devices to resolve problems
___ Inspect storage facilities (secure with limited access) as appropriate
___ Verify process to calculate dosage and confirm accuracy of preparation; verify proper use/setting of device controls as applicable

Regulatory Issues

___ Check study files to ensure all necessary documents are included (signed protocol page and protocol, amendments, consent form, IRB/IEC approval and correspondence)
___ Ensure continuing IRB/IEC notification/reporting as appropriate to include periodic IRB/IEC renewals, protocol amendments, and safety reports
___ Verify that informed consent procedures are being followed and that a valid consent form is present for each subject
___ Collect any new or revised regulatory documents

Laboratory Issues

___ Review protocol-specific laboratory requirements
___ Review laboratory certificates for current date
___ Ensure proper handling of all laboratory specimens
___ Resolve any problems related to the collection of samples or the performance of local, central, or core laboratories

Responsibilities of Site Study Personnel

___ Review responsibilities of site personnel to determine if changes in personnel or responsibilities have occurred since the last monitoring visit
___ Provide training for site personnel when needed, including new study personnel, changes in study procedures, or a change in the conduct of the study such as a protocol amendment

Serious Adverse Event (SAE) Status

___ Review SAEs that occurred at the site
___ Obtain additional SAE information from site as needed
___ Ensure that all SAEs have been reported accurately and appropriately

Source Document Review/Verification of Data

___ Verify accuracy of recorded data as compared to source documents
___ Review data forms for incorrect data, omissions, and out-of-range variables
___ Review source documents for adherence to protocol
___ If paper data forms are used, collect original copies of completed data forms
___ Generate data queries
___ Obtain responses to outstanding data queries

Outstanding Issues

___ Determine actions to be taken by the site for outstanding or unresolved issues
___ Determine actions to be taken by the sponsor for outstanding or unresolved issues

Meet with PI and CRC

___ Discuss overall progress of trial
___ Discuss new developments affecting subject safety/conduct of trial
___ Discuss outstanding issues and actions to be taken by the site and/or sponsor
___ Sign Site Visit Log

- discuss plans for record retention;
- discuss plans for notifying PI and subjects of final study results.

In some trials, the activities performed to close out a study site are conducted via telephone or written communication rather than during an on-site visit. When this occurs, sites will be provided with the necessary information and forms (or electronic records) to complete this process. The PI and the CRC should make sure that all contractual agreements have been met and payments to the site have been made. Any outstanding issues from previous monitoring visits should be resolved to the satisfaction of the sponsor and PI. The PI is required to write a letter or final study report to the sponsor and to the IRB, documenting the number of subjects enrolled, any AEs not previously reported, and any other information relevant to the site. A copy of this letter should be kept in the study file.

Documenting Monitoring Visits

After each monitoring visit, the CRA's findings will be discussed with the PI and CRC. If any problems or areas of concern are identified during the monitoring visit, these should be discussed, and corrective actions and timelines agreed upon by the PI, CRC, and the CRA. Before leaving the site, the CRA will sign and date the Site Visit Log, the form used at the site to keep a record of monitoring visits. The name of the CRA, dates of the visit, and the purpose of the visit (e.g., initiation, periodic monitoring, or close-out) will be recorded by the CRA on the log; Site Visit Logs should be kept in the site study file.

Site Visit Report/Trip Report

After the monitoring visit has been completed, CRAs submit a comprehensive site visit report (often called a "trip report") to the sponsor or sponsor-designee. This report lists all findings at the site. Any problems, protocol violations, or other issues will be described, as well as proposed corrective actions and timelines for making the changes.

Follow-up Letter to the PI

Findings from the site visit will be summarized in a follow-up letter or progress report to the PI at the study site. The PI and CRC should review the letter to make sure they agree with the stated findings and suggestions to resolve deficiencies or corrective actions, if any. The follow-up letter should then be kept in the site study file.

Figure 7.2 Sample Follow-up Letter

July 15, 2009

Dear Dr. Candoit,

A monitoring visit for HEAT was conducted at your site on July 15, 2009. During this visit, I reviewed CRFs and associated source documents for 8 of the subjects enrolled at your site. I also reviewed your regulatory documents file and drug accountability records. Your study coordinator was very helpful in answering my questions and worked cooperatively to resolve CRF discrepancies identified through source document verification of the recorded data.

The following issues were identified at this visit:

- On one subject, baseline laboratory values were not obtained within 24 hours of randomization (subject #6 had results from 28 hours before randomization).
- A 12-lead ECG was not obtained at discharge on subject #3 as required by protocol.
- The Investigators' Brochure and a blank copy of your IRB-approved consent form must be placed in your regulatory file.

Your site has done an excellent job of enrolling subjects and performing protocol-required procedures in this trial. The CRFs were completed with a high degree of accuracy and consistency, and all source documents were available for my review.

I thank you and your study coordinator for your time and assistance during this visit. Please call me if you have any questions about the above noted items or any other concerns or questions you may have.

Sincerely,

Your Clinical Research Associate

In-House Monitoring

With the technological advances that make possible the electronic recording and transmission of study data, an increasing proportion of data monitoring is being done "in-house" at the sponsor's location or data center. This may be done before, after, or instead of on-site monitoring. Regardless of whether data are submitted on paper CRFs or electronically via eCRFs, some type of in-house review will be performed. This may include: 1) computerized checks, and/or 2) source document verification of SAEs and study endpoints.

Computerized Checks

Regardless of whether data forms are submitted as paper forms or as electronic records, computerized checks can provide automatic verification of some data fields. When paper data forms are submitted to the data center, the data will be entered into an electronic database by data center or sponsor personnel; when eCRFs are used, the data are sent to the data center or sponsor electronically rather than on paper.

Computerized checks can be performed on: 1) blank fields in the data forms, 2) data that are outside a prespecified range, and 3) data that are inconsistent with other data recorded on the data forms. Sponsors will usually provide conventions for how to fill in blanks where no data exist, for example, ND (No Data or Not Done) if a test was not performed or NA (Not Applicable) if a data field does not apply to a specific subject (e.g., a pregnancy test for a male subject). Data that fall outside a prespecified range will generate a query based on an expected range. For example, a heart rate recorded as "48 beats per minute" may be queried because the expected range was established as 50–110 beats per minute. Data that are inconsistent with data recorded elsewhere in the data forms may be queried; for example, when the medication page notes that a medication was discontinued because of hypotension, but hypotension is checked "No" on the AE page, a query will be generated.

Computerized checks are set up according to prespecified rules and ranges. Sometimes data that are queried as a result of computerized checks are actually correct; the example of the heart rate of 48 beats per minute noted above might represent accurate data. The computerized query requests the CRC to confirm the existing data or to provide corrected data.

Source Document Verification Done at the Sponsor or Data Center

Trial sponsors sometimes require sites to submit data forms and supporting medical records (source documents) for review of SAEs or study endpoints. In some trials, the SAE source documents are couriered to the sponsor or data center, where source document verification can be done by the safety committee. Because interpreting endpoint data is critical to the analysis and reported results of a clinical trial, endpoint review and adjudication may be performed to eliminate investigator variability in reporting events. Some sponsors establish an impartial group of clinicians (a Clinical Endpoints Committee, or CEC), to review data forms and source documentation

for specified events to determine whether an endpoint has been reached based on preestablished criteria. Please refer to Chapter 14 for further discussion of endpoint adjudication.

Protected Health Information

When source documents must be submitted to the sponsor or data center, the source documents must be de-identified (redacted) to separate the data from any identifying information linking the data to the specific subject. Source documents should have identifiers blocked out with a permanent marker and be labeled with the subject trial number and initials used on the subject data forms.

Identifiers that must be removed or marked out on source documents include but are not limited to:

1 Name
2 Mailing address
3 E-mail address
4 Telephone and fax numbers
5 Social security or other national identification numbers
6 Medical record/case note numbers
7 Vehicle license plate numbers
8 Biometric identifiers such as fingerprints
9 Images that allow the identification of a subject

Audits and Inspections

In addition to on-site monitoring visits by CRAs, other groups may conduct visits at the investigative site. A sponsor may perform an *audit*, or quality assurance visit, at the site to ensure that proper documentation of processes and procedures are in place, and to review subject records and data forms. Audits differ from monitoring visits in that audits focus on whether trial-related activities were done in compliance with regulations, GCP, and sponsor and site SOPs.

Federal regulations governing clinical research give the FDA the authority to perform *inspections* at the clinical sites. Inspection activities are similar to those performed at audits, but include a review of the sponsor activities and responsibilities, as well as those of the investigator.

Audits and Inspections in the Regulations and Guidelines

Audits and inspections are included in regulations, as well as in ICH guidelines.

- *Form FDA 1572 Statement of Investigator. Investigator Commitment.* The PI agrees in writing 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.
- *21 CFR 312.68 (Drugs). 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.
- *21 CFR 600.20 Inspectors (Biologics).* Inspections shall be made by an officer of the FDA having special knowledge of the methods used in the manufacture and control of products and designated for such purposes by the Commissioner of Food and Drugs, or by any officer, agent, or employee of the Department of Health and Human Services (DHHS) specifically designated for such purpose by the Secretary of the office of DHHS.
- *21 CFR 812.145 Inspections (Devices). Entry and inspection.* A sponsor or an investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
- *ICH E6: Sponsor, item 5.19.1.* The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Sponsor Quality Assurance Audits

Why Do Sponsors Audit a Clinical Trial?

1. To ensure that the monitors are performing their job accurately;
2. To ensure that investigators and staff are performing their jobs appropriately;
3. To prepare for future regulatory inspections; and
4. To assure that data for regulatory submission will be suitable.

During or after a trial, auditors from the sponsor (or sponsor designee) may visit selected sites to conduct quality assurance audits. These audits ensure that the CRA and site study staff are performing their duties according to regulations, the protocol, and the site's SOPs. Sponsor audits also help to prepare for future FDA inspections and assure that data are suitable for a marketing application (i.e., a New Drug Application, Biologics License Application, or a Premarket Approval for a device). These visits are much like periodic monitoring visits, and should be viewed by the PI and CRC as an opportunity to improve trial management at their site. Sponsor audits are common practice in clinical trials for which an Investigational New Drug (IND) application has been submitted.

Sponsors may also conduct audits if they are concerned that an investigative site is out of compliance with the regulations or protocol. The sponsor should determine whether there is evidence of noncompliance, and if so, take corrective action to bring the site into compliance, or terminate the site from study participation.

A typical audit lasts from 1–2 days; the PI will be given an agenda and a list of data forms and documents needed for review, including the study file and IRB records. Subject data forms, electronic data records, source documents, site study files, and signed consent forms may be reviewed, as well as drug/biologic/device storage and accountability records. Regulatory documents are typically reviewed to ensure that IRB approval was obtained and documented before initiating the study, that informed consent was obtained from each subject before beginning any study procedures, that education and training of applicable personnel was performed and documented, and that proper investigational product use or administration procedures were followed and documented.

Auditors will review study records to ensure that an *audit trail* exists. An audit trail allows data to be followed from the subject, to data forms, to the data center and sponsor, and through data processing and analysis to the final written report. This is particularly important when data are changed or corrected after the initial submission of data by the investigative site. Records must be kept for all original and corrected data, with an indication of who made the changes and when the changes were made.

Information from an audit is typically for internal use by the sponsor, and often the site is not given a copy of the audit report. However, the PI may be informed of the overall results of the audit and whether the trial data are or are not acceptable.

FDA Inspections

The FDA's Bioresearch Monitoring Program is a comprehensive program that includes on-site inspections and data audits. First initiated in 1977, this program addresses the need for regular inspections to ensure data quality and integrity when new product applications are submitted for approval. The Monitoring Program regulates inspections of clinical investigators, IRBs, sponsors, CROs, and AROs.[4]

The FDA is authorized by law to inspect clinical sites conducting trials under an IND application (for drugs and biologics) or an IDE application (for devices) at any point during the trial. Inspections can occur even after the site has completed participation in the trial and results have been submitted for marketing approval.

When an investigative site is selected for an inspection, the FDA will usually contact the PI by telephone to arrange a mutually acceptable time for the visit. Sponsors often request that PIs notify them when contacted about an upcoming FDA inspection. Sponsors may want to help the site prepare for an FDA inspection to ensure that it runs smoothly.

Upon arrival at the clinical site the inspector will show credentials (photo ID) and present a Form FDA 482, *Notice of Inspection* to the investigator.

The inspection usually begins by determining the facts surrounding the conduct of the study:

- What delegation of authority has occurred;
- Who has responsibility for the various activities;
- Where specific aspects of the study were performed;
- How and where data were recorded;
- How test product (drug/biologic/device) accountability was maintained;
- How the CRA communicated with the PI; and
- How the CRA evaluated the study's progress.[5]

The FDA inspector has the right to access and copy study records. Subject data forms are compared with source documents that support the data. The inspector may examine subject records that pre-date the study to determine whether the medical condition being studied was properly diagnosed, and whether an interfering medication was given before the study began. Records covering a reasonable period after completion of the study may also be reviewed to determine whether proper follow-up was conducted and whether all signs and symptoms reasonably attributable to the product's use were reported.

Figure 7.3 Sample of a Notice of Inspection – Form FDA 482

and the employees of the person, the procedures used by the person for handling confidential information, the compensation arrangements made by the person, and the procedures used by the person to identify and avoid conflicts of interest. Upon the request of an officer or employee designated by the Secretary, the person shall permit the officer or employee, at all reasonable times, to have access to, to copy, and to verify, the records.

Section 512 (l)(1) In the case of any new animal drug for which an approval of an application filed pursuant to subsection (b) is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to experience, including experience with uses authorized under subsection (a)(4)(A), and other data or information, received or otherwise obtained by such applicant with respect to such drug, or with respect to animal feeds bearing or containing such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) or subsection (m)(4) of this section. Such regulation or order shall provide, where the Secretary deems it to be

from the notification requirements has been granted by the Secretary under section 359(a)(2) or 359(e)."

(b) "Every manufacturer of electronic products shall establish and maintain such records (including testing records), make such reports, and provide such information, as the Secretary may reasonably require to enable him to determine whether such manufacturer has acted or is acting in compliance with this subpart and standards prescribed pursuant to this subpart and shall, upon request of an officer or employee duly designated by the Secretary, permit such officer or employee to inspect appropriate books, papers, records, and documents relevant to determining whether such manufacturer has acted or is acting in compliance with standards prescribed pursuant to section 359(a)."

* * * * * *

(f) "The Secretary may by regulation (1) require dealers and distributors of electronic products, to which there are applicable standards prescribed under this subpart and the retail prices of which is not less than $50, to furnish manufacturers of such products such information as

and locate, for purposes of section 359, the
ucts for purposes other than resale, and (2)
reserve such information Any regulation
pursuant to clause (1) of the preceding
such dealers and distributors to elect, in lieu
ch information to the manufacturer to hold
ion until advised by the manufacturer or
ation is needed by the manufacturer for
d (B) provide that the dealer or distributor
ection, give prompt notice of such election
ntifying the notifier and the product) to the
advised by the manufacturer or Secretary,
purposes of Section 359, immediately furnish
quired information. If a dealer or distributor
distribution of electronic products, he shall
e manufacturer. Any manufacturer receiving
subsection concerning first purchasers of
han resale shall treat it as confidential and
or the purpose of notifying persons pursuant

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fail or to refuse to establish or maintain
art or to permit access by the Secretary or
epresentatives to, or the copying of, such
nspection, as required or pursuant to section

* * * * * *

ection

eneral, with the approval of the Secretary, is
rce such regulations as in his judgment are
introduction, transmission, or spread of
m foreign countries into the States or
tate or possession into any other State or
carrying out and enforcing such regulations,
provide for such inspection, fumigation,
extermination, destruction of animals or
cted or contaminated as to be sources of
an beings, and other measures, as in his

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

1. DISTRICT OFFICE ADDRESS & PHONE NO.

TO

2. NAME AND TITLE OF INDIVIDUAL

3. DATE

4. FIRM NAME

5. HOUR a.m. p.m.

6. NUMBER AND STREET

7. CITY AND STATE & ZIP CODE

8. PHONE # & AREA CODE

VOID

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)][1] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264][2]

9. SIGNATURE *(Food and Drug Administration Employee(s))*

10. TYPE OR PRINT NAME AND TITLE *(FDA Employee(s))*

[1] **Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:**

Sec. 704. (a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any person (excluding farms and restaurants) who manufactures, processes, packs, transports, distributes, holds, or imports foods, the inspection shall extend to all records and other information described in section 414 when the Secretary has a reasonable belief that an article of food is adulterated and presents a threat of serious adverse health consequences or death to humans or animals, subject to the limitations established in section 414(d). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, or restricted devices are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use or, restricted devices which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this Act), and research data (other than data relating to new drugs, antibiotic drugs and devices and, subject to reporting and inspection under regulations lawfully issued pursuant to section 505(i) or (k), section 519, or 520(g), and data relating to other drugs or devices which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 505(j)). A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

Sec. 704. (a)(2) The provisions of the third sentence of paragraph (1) shall not apply to (A) pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not, either through a subsidiary or otherwise, manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail; (B) practitioners licensed by law to prescribe or administer drugs, or prescribe or use devices, as the case may be, and who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices solely for use in the course of their professional practice; (C) persons who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices solely for use in research, teaching, or chemical analysis and not for sale; (D) such other classes of persons as the Secretary may by regulation exempt from the application of this section upon a finding that inspection as applied to such classes of persons in accordance with this section is not necessary for the protection of the public health.

Sec. 704. (a)(3) An officer or employee making an inspection under paragraph (1) for purposes of enforcing the requirements of section 412 applicable to infant formulas shall be permitted, at all reasonable times, to have access to and to copy and verify any records (A) bearing on whether the infant formula manufactured or held in the facility inspected meets the requirements of section 412, or (B) required to be maintained under section 412.

Sec. 704. (b) Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary.

Sec. 704. (c) If the officer or employee making any such inspection of a factory, warehouse, or other establishment has obtained any sample in the course of the inspection, upon completion of the inspection and prior to leaving the premises he shall give to the owner, operator, or agent in charge a receipt describing the samples obtained.

Sec. 704. (d) Whenever in the course of any such inspection of a factory or other establishment where food is manufactured, processed, or packed, the officer or employee making the inspection obtains a sample of any such food, and an analysis is made of such sample for the purpose of ascertaining whether such food consists in whole or in part of any filthy, putrid, or decomposed substance, or is otherwise unfit for food, a copy of the results of such analysis shall be furnished promptly to the owner, operator, or agent in charge.

Sec. 704(e) Every person required under section 519 or 520(g) to maintain records and every person who is in charge or custody of such records shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and to copy and verify, such records.

Section 704 (f)(1) An accredited person described in paragraph (3) shall maintain records documenting the training qualifications of the person

FORM FDA 482 (7/06) PREVIOUS EDITION IS OBSOLETE (Continued on Reverse) NOTICE OF INSPECTION
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Study-Directed Inspections

Study-directed inspections are conducted for trials that are pivotal to product marketing applications such as a New Drug Application, Biologics License Application for biological products, and a Premarket Approval application for medical devices. The sites selected for inspection tend to be the sites that have enrolled the most subjects or participated in the most studies of the investigational product.

During these visits, the inspector examines the reported data, giving particular attention to protocol adherence and data integrity. Documentation of informed consent, IRB approval, and continuing review of ongoing studies are also verified.

Investigator-Directed Inspections

This type of inspection may be initiated if the sponsor or FDA has concerns about an investigator or if there is a complaint from a subject about human subject protection violations. Other reasons for investigator-directed inspections include situations where investigators have participated in many trials of the test product, enrollment was much higher and faster than anticipated, or site data are inconsistent with data from other sites. The investigator-directed inspection goes into greater depth than a study-directed inspection, covers more case reports, and may span more than one study.

If an investigator fails in his/her obligations, the FDA can reject the study, disqualify the investigator from participating in additional studies, impose restrictions on carrying out future studies, and in the case of research misconduct, pursue criminal prosecution.

Inspection Findings and Reports

The FDA conducts an exit interview at the end of all inspections. At this interview, the inspector discusses the findings of the inspection, clarifies misunderstandings, and if it is indicated, may issue the investigator a written Form FDA 483, *Inspectional Observations*, documenting deviations from the regulations. If the investigator disagrees with any of the findings or believes there was a misunderstanding, the investigator should provide the inspector with an explanation of why the investigator believes the observation is not a violation. The investigator must convey the explanation carefully so as to keep a positive, open line of communication with the inspector.

Once the findings have been reviewed and discussed with the investigator, the inspector will submit an *Established Inspection Report* to the FDA, where it will be reviewed and assigned a final

Research Misconduct

Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Honest errors or differences of opinion are not considered to be research misconduct.

Fabrication – making up data or results and recording or reporting them.

Falsification – the manipulation of research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

Plagiarism – the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.[6]

Figure 7.4 Sample of an Inspectional Observations Form – Form FDA 483

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
	FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO:

FIRM NAME	STREET ADDRESS
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) ~~(WE)~~ OBSERVED:

List your observations in a logical manner

VOID

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED

FORM FDA 483 (4/03) PREVIOUS EDITION OBSOLETE **INSPECTIONAL OBSERVATIONS** PAGE 1 of 1 PAGES

PSC Media Arts (301) 443-1090 EF

Examples of Common Findings of Audits and Inspections

Common findings in audits and inspections center on several areas:

- Lack of PI oversight and inappropriate delegation of responsibilities
- Informed consent:
  - Stamped PI signature
  - Missing signatures
  - Missing dates
  - Use of incorrect version of consent form
  - Missing elements in the consent form
  - Lack of a written note in medical record or clinic note documenting consent
- Protocol:
  - Ineligible subjects enrolled
  - Protocol-specified tests not done
  - Use of unapproved concomitant medications
- IRB:
  - Missing IRB approval for protocol amendment or revised consent form
  - Lack of reporting to the IRB
  - Expired study approval
- Data and Study Records:
  - Data changes not properly made
  - Source documents not available
  - Lack of consistency between source documents and recorded data

classification. Written notification of the issues will be submitted to the investigator in the form of one of the following:

- *NAI (No Action Indicated):* No objectionable conditions or practices were found during the inspection (or the objectionable conditions found did not justify further action). A letter will be issued that requires no response from the site.
- *VAI (Voluntary Action Indicated):* Objectionable conditions or practices were found but the FDA is not prepared to take or recommend any administrative or regulatory action. A letter may be issued at the discretion of the FDA depending on the nature of the deviations. This letter may or may not require a response from the investigator; however, if a response is required, the letter will describe what is necessary.
- *OAI (Official Action Indicated):* Regulatory and/or administrative actions will be recommended. This may include issuance of a

"Warning Letter" identifying deviations requiring immediate action by the investigator. The FDA may inform both the study sponsor and the site IRB of the deficiencies. They may also inform the sponsor if procedure deficiencies indicate ineffective monitoring by the sponsor.

Investigator Response

The Warning Letter issued when official action is indicated will specify how quickly the investigator needs to respond, usually within 15 working days. The investigator's response should address each observation and indicate the corrective action taken or the proposal for corrective action, including the proposed time period for completion. The tone of the letter should be factual, professional, and cooperative. Depending on the investigator's response, the FDA may require additional follow-up. If the deviations are significant violations of applicable regulations, the FDA can recommend additional sanctions.

References

1 21 CFR 312.50, 21 CFR 812.40
2 "Improve Quality With a Trial Monitoring Program" *Clinical Trials Administrator* November 2005; 127–130
3 ICH E6. Glossary 1.51 and 1.52
4 http://www.fda.gov/ora/compliance_ref/bimo/background.html
5 http://www.fda.gov/OC/OHRT/IRBS/investigator.pdf
6 http://ori.dhhs.gov/policies/documents/ViewPublication-VAMisconduct.pdf

8 The Principal Investigator, the Clinical Research Coordinator, and the Study Site

In this Chapter

- Rewards and challenges of participating in clinical research
- Building a team for clinical trials
- The space and resources needed for conducting clinical trials

"It is one of the most beautiful compensations of life, that no man can sincerely try to help another without helping himself."

Ralph Waldo Emerson (1803–1882), American writer; founder of Transcendentalist movement

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

Becoming an investigator in clinical trials can be a highly rewarding experience. It broadens one's perspective in the practice of medicine and allows people to participate in testing the newest medical treatments. Participation in clinical trials affords opportunities for interaction with medical science "thought leaders;" moreover, site investigators may be able to contribute to the authoring of publications of study results. Working with patients who are enrolled as subjects in a clinical research project may prove to be especially in-depth and rewarding when compared with patient interactions in more typical practice settings. This can be especially true when conducting long-term follow-up clinical trials. These positive outcomes are just some of the benefits that result from the dedicated effort it takes to successfully conduct clinical trials.

While the positive aspects of being a principal investigator (PI) are significant, the responsibilities and accountability are equally important and can present the investigator with many challenges. In recent years, attention has focused on researchers who fail to ensure that subjects fully understand the possible risks of a study, or who do not comply with the standards of good clinical practice (GCP). Enrolling subjects who do not meet study eligibility criteria, neglecting to report adverse events (AEs) as required, not following the protocol, and not providing proper training for staff are some of the concerns that have been associated with inadequately trained and prepared PIs. In order to counter these problems, opportunities for education and training have been expanded to ensure that all investigators, research administrators, Clinical Research Coordinators (CRCs), Institutional Review Board (IRB) members, and other study personnel have appropriate training in bioethics and other research-related issues involving human subjects.

These issues underscore the fact that although involvement in clinical research is a challenging and rewarding experience for many, it is not for everyone. Physicians who are considering serving as an investigator in clinical trials must carefully consider a number of research-related aspects that affect this decision. To successfully conduct clinical trials, PIs must have the time to perform the oversight required, and should evaluate how this research can best be incorporated into their health care practice.

Investigator

Investigator is generally defined in the regulations as the "individual who actually conducts a clinical investigation or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team."
21CFR 56.102(h) and
21 CFR 812.3(i)

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 the subjects under the investigator's care; and for the control of the drugs under investigation.
21 CFR 312.60

The Principal Investigator

Health care providers enjoy participating in clinical research for a wide variety of reasons. Personal motivations include the opportunity to stay abreast of the latest treatments in one's specialty area, the

ability to offer new products to patients, and the chance to meet and exchange ideas with colleagues involved in clinical trials. In addition, investigators may be able to enlist the support of others in the medical practice or hospital to broaden the clinical research opportunities available throughout the institution.

While it is rewarding to be able to offer new treatment opportunities to patients, it is important to note that not all subjects participating in clinical trials personally benefit from the test product in the study. Personal benefit to the individual will not occur if the subject is given placebo or a study drug dose that proves to be subtherapeutic; no benefit occurs when an investigational device proves ineffective. However, even when subjects participating in clinical research do not benefit from the treatment under investigation, many subjects do benefit from the increased contact with the investigator, CRC, and other study personnel (although it should be stressed that these benefits are tangential to the research itself). Additionally, the knowledge gained from an individual's participation adds to a body of knowledge that other physicians will draw upon in caring for future patients with the same disease process.

When randomization is involved in a clinical trial, the investigator must be free from bias regarding the scientific question being addressed by the protocol. For instance, if a randomized study is being conducted to compare a standard therapy with a novel treatment, and the investigator believes at the outset that one therapy is superior to the other, then that investigator already has a bias regarding the study and should not be participating as an investigator in the trial. *Clinical equipoise*, which describes the situation that occurs when a lack of consensus exists among health care experts regarding a scientific or therapeutic question, requires investigators to remain objective when participating in clinical trials.

Adhering to a protocol may require the physician-investigator to perform procedures or treat subjects in ways that differ from his or her standard clinical practice. While subject safety must of course be foremost in the investigator's mind, following the protocol carefully is critical to determining whether the new treatment or product is truly safe and effective. This can sometimes result in the early termination of a subject's participation in a study to ensure the subject's safety and well-being.

Some Investigator Tasks and Time Commitments

- Orienting medical partners and staff to the protocol
- Adapting office and clinical practice routines (and/or documentation of routines) to the protocol requirements
- Attending Investigator Meetings
- Screening, enrolling, and consenting subjects
- Communicating with the CRC, site study staff, and sponsor (or sponsor-designee)
- Performing study-related procedures and follow-up visits
- Reviewing subject data

Characteristics of an Effective Principal Investigator

Participating in clinical trials requires a substantial time commitment. While the PI may delegate many research-related tasks to

members of the study staff, including the CRC and subinvestigators, the PI is still ultimately responsible for the conduct of the study and for maintaining subject safety. In order to ensure the integrity of the study, as well as adherence to the protocol and reporting requirements, the PI must remain fully engaged and informed throughout the trial. By demonstrating trust, respect, and support for the CRC and other study personnel, the PI will help to ensure a successful study.

Successful PIs have several common characteristics:

1 *Extensive knowledge in the field of medicine/subspecialty area under study.* The PI should have sufficient knowledge of the area of medicine or treatment under study to be able to perform a thoughtful review of the background information in the protocol and evaluate the clinical question being asked. The PI must be thoroughly familiar with the investigational product as described in the protocol and Investigator's Brochure. A knowledgeable investigator will be able to anticipate and recognize problems, and make appropriate decisions about the clinical care of subjects.

2 *Good communication skills.* While the PI has ultimate responsibility for the conduct of the clinical trial at the site, he or she may delegate many activities to other team members, including the CRC, subinvestigator, and support staff. The PI must be able to communicate clearly and effectively with all team members to ensure that everyone understands their delegated activities; communication should occur at regularly scheduled times as well as on an *ad hoc* basis. When approaching potential subjects for consent to participate, the PI must be able to explain study activities and procedures in language that can be understood by the subject, and must do so without exerting undue influence.

3 *Awareness of GCP and regulatory responsibilities.* An effective PI knows the regulations that govern clinical research and understands the requirements to personally supervise the study and to protect the rights, safety, and welfare of study subjects. The PI must be familiar with GCP guidelines and the regulatory requirements for data collection, AE reporting, and record retention, and must understand the proper methods for handling and storing test products.

4 *Openness to new concepts and ideas.* A PI who is open to suggestions from the CRC and other team members regarding the conduct of the study will have a greater chance of success. Because the CRC is often the person performing many daily study activities, the CRC may have useful suggestions about a different approach to a problem; for example, how to recruit more subjects.

The PI should also be open to new ideas generated by colleagues and PIs at other sites.

5 *Integrity.* The PI's integrity is of the utmost importance. The PI must possess the integrity to follow the protocol in enrolling only eligible subjects, even when recruitment is difficult or below expectations. The PI must follow all regulations and ensure that study team members do so as well. Integrity comes into play in many situations; for example, when a subject experiences a serious adverse event (SAE) and needs to discontinue study participation, the PI must put the welfare of the subject above that of the study.

6 *Appreciation of work done by team members and others.* Finally, the PI must be able to recognize and appreciate the study-related work done by other team members. The CRC who screens subjects, completes data forms, and works with the study monitor; the laboratory technician who processes samples; and the secretary who photocopies documents, schedules appointments, and greets representatives from the sponsor, all do so with a commitment to the research but usually without authorship on journal publications or more public forms of recognition. Acknowledging the crucial contributions of these team members is important to building team commitment and support.

Conflict of Interest

A conflict of interest (COI) exists when someone has an interest that may compromise their ability to remain impartial and objective. In clinical trials, the potential for a COI exists in many aspects of clinical research and occurs when someone uses his or her position for personal or financial gain. One common source of conflict arises when a physician or researcher has a financial interest that is connected in some fashion to the clinical trial. Physicians and researchers often have financial agreements with pharmaceutical companies and entities that fund clinical research. These financial agreements can include speaking fees ("speaker's bureau"), travel stipends, research grants, consulting fees, and more.

A COI does not necessarily imply conscious wrongdoing; a COI exists when there is the possibility or likelihood of a relationship affecting someone's impartial judgment. In clinical trials, a COI can arise when a physician who owns stock in a pharmaceutical company participates as a PI in a study of the company's product. In spite of efforts to remain impartial, it would be difficult for the PI to maintain objectivity because of the possibility of financial gain if the study is a success.

COIs are not always based on financial gain. A COI may occur when there is opportunity for personal or professional gain; for example, an investigator's desire for authorship on a study publication or for recognition for enrolling the most subjects overtakes his or her responsibility for protocol adherence and enrolling only subjects who meet all eligibility criteria. Another source of COI involves protocols that compete for access to the same subject population. An investigator recruiting subjects for multiple trials investigating the same patient population has a potential COI when the PI has a relationship (financial or otherwise) with the sponsor of one trial; such a relationship could lead to the PI being biased toward enrolling subjects into that sponsor's study.

Disclosure of Conflict of Interest

To minimize or eliminate financial COI, regulations have been enacted regarding the disclosure of potential sources of conflict. Financial disclosure regulations are contained in 21 CFR 54 and apply to investigators, subinvestigators, and all other study team personnel identified as having direct involvement in the treatment or evaluation of research subjects. Financial disclosure is also required for spouses and dependent children of these identified investigators.[1] While disclosure itself does not eliminate COI, by making financial relationships known to the FDA, potential sources of COI can more readily be identified.

Management of Conflict of Interest

There are a number of methods to manage disclosed COIs. Institutions may establish a committee to review and make recommendations regarding disclosed COIs. The institutional committee may develop policies for handling COIs, such as requiring information pertaining to the source of funding and/or financial arrangement in the informed consent document or requiring someone other than the investigator with the disclosed COI to obtain informed consent from subjects.[2] Investigators may need to sell stocks or place them in a blind trust, decline the role of a paid speaker, or refuse to accept gifts and hospitality from the study sponsor.

Ideally, at any given time, a PI participates in only one trial drawing upon a specific subject population. However, if this is not possible, the PI should develop an objective system for enrolling subjects in competing protocols.

If a PI is also a member of an IRB, a COI exists if the PI is allowed to vote on his or her own protocol. To prevent this, IRB regulations require any member who is a part of a clinical study team to be excluded from participating in IRB deliberations regarding the protocol.

IRBs members may not participate in the initial or continuing review of research for which the IRB member has a conflicting interest, except to provide information as requested by the IRB.[3] In addition, the IRB member should not be present for the discussion and voting on the research project.

Investigator Delegation of Study Activities

Investigators may choose to delegate a number of study-related activities to other members of the site study team. PIs often delegate many activities to the CRC, who can focus full attention on the daily tasks and procedures of clinical trials. The PI must realize, however, that the responsibility and accountability for the conduct of the study remains solely with the PI. It is the PI's responsibility to ensure that all study team members have the training and information needed to perform study activities. Only the PI can sign the Form FDA 1572 used in drug and biologics trials; this is also true for the investigator agreement between the PI and the sponsor in device trials where a Form FDA 1572 is not used.

Staffing to Support Clinical Trials

A study site cannot effectively and efficiently participate in clinical trials without sufficient staff. Not only does the site need an adequate number of personnel, but all personnel must also be trained appropriately. Regulations require that the PI ensure that all study staff are adequately trained in study-related activities and kept up-to-date about study-related information.

Activities performed by study personnel may vary from one trial to another depending on many study-specific factors; however, there are general personnel needs that apply to most trials. A CRC, subinvestigators, and support personnel can all work closely with the PI to ensure that the study meets regulatory requirements and GCP standards, including the protection of human subjects and subject confidentiality.

Clinical Research Coordinator

In particular, the role of the CRC is vital to the success of a trial. A CRC specializes in working on clinical trials and handles many of the study activities under the direction of the PI. CRCs may come from a

IRB Members and Conflict of Interest

While U.S. regulations require the disclosure of COI for investigators, there currently is no consistent method for voting IRB members to disclose potential COIs and relationships with industry. While some IRBs require disclosure by members to the full IRB, others require disclosure to the IRB chairperson, and yet others disclose COI information to a separate entity within the institution; many IRBs do not have any requirements for COI disclosure. Of those IRBs with disclosure requirements, many do not have written policies for how to manage the disclosed COIs of their members. This is inconsistent with the current COI guidance for personnel involved in clinical trials and may lead to lapses in awareness of these conflicts when IRB members vote on protocols.[4]

variety of backgrounds, including nursing, pharmacy, and other medical fields. A medical background makes it easier to be effective in this role, since a CRC with such experience will be familiar with the clinical environment and medical language, and will have experience interacting with patients and research subjects. When CRCs come from a nonmedical background, additional training may be required before the CRC becomes fully proficient. CRCs from a nonmedical background may be restricted from performing protocol-related activities that require a license or certificate to perform. For example, depending on local state and institution policies, study personnel who will draw or process blood samples, or dispense and administer medications, may be required to have a nursing license or other type of licensure or certification.

CRCs may share many of the same personal and professional motivations for working in clinical trials as the PI. They may be eager to learn about novel treatments and may enjoy the opportunity to work with patients being offered these new products. CRCs may value the experience of working with like-minded colleagues within their own institution as well as with colleagues at other institutions across the nation or even around the world.

CRCs often gain much of their knowledge through on-the-job training, by working with others who have experience in clinical trials. Knowledge about clinical trials can also come from local, national, or international courses, books, and online sources. Protocol-specific training may be done at Investigator Meetings as well as on-site by monitors. Clinical research education and training courses may be offered by the hospital or local university where the CRC is employed. There are also professional organizations for CRCs, including the Association of Clinical Research Professionals (ACRP) and the Society of Clinical Research Associates (SoCRA). These organizations conduct annual national and international meetings, training courses, and certification examinations. The Drug Information Association (DIA) also has conferences on clinical research topics and provides opportunities for training. Several online clinical research resources that provide opportunities for education and training are available, including the Collaborative Institutional Training Initiative (CITI) and Clinical Trials Networks (CTN) Best Practices Web sites. CRCs may check local hospitals, universities, and colleges for training programs and courses. Local hospitals or institutions may have established CRC networks or organizations to provide education, support, and career advancement opportunities.

Training and Educational Opportunities for CRCs

ACRP	http://www.acrpnet.org
SoCRA	http://www.socra.org
DIA	http://www.diahome.org
CITI	http://www.citiprogram.org
Clinical Trials Networks Best Practices	http://www.ctnbestpractices.org

The specific activities delegated to the CRC by the investigator vary according to the needs of a particular trial, but for all trials, the delegation of activities should be discussed well before the trial begins, and a plan for regular communication and review of activities should be in place.

It is easy to underestimate the time required to perform these activities. One particularly common mistake is the assumption that these duties can be performed during a lunch break, or in addition to other full-time job responsibilities. A CRC working part-time may be a realistic option for some trials and activities, but in order to work effectively, even the part-time CRC should be available during business hours to meet with subjects, talk with sponsor representatives, and perform other study-related tasks.

Some trials have challenging entry criteria that can make screening subjects a laborious process. In many trials, protocol adherence and data collection is complex and detailed. Being aware of these issues allows the PI to find creative ways of providing incentives that can help prevent "burnout" among personnel who devote significant time and effort to a trial. These incentives can be as substantial as providing transportation to a professional meeting or establishing an education grant, or as simple as a lunch or other form of acknowledgement. Some forms of recognition are considered compensation; the dollar value is reported as income to be counted in total wages. When the PI plans to provide recognition that has a currency value, the PI should first check with the human resources personnel to identify any financial or tax consequences for study team members who receive it. When study team members feel appreciated and remain enthusiastic about a study, subject enrollment and follow-up will benefit. The work performed early in a study (preparation of materials for IRB review, orientation of site staff, development of data worksheets, etc.) will pay off in increased enrollment, while the work performed throughout the remainder of the study (completing data forms, reporting AEs,

Activities Commonly Performed by CRCs

Some of the tasks that are often delegated to the CRC include:

1. Review of new protocols to evaluate the feasibility of conducting the study at the site.
2. Development of a study budget.
3. Preparation and submission of documents to the site IRB, the sponsor, and/or other regulatory agencies.
4. Education and training of site personnel who directly interact with study subjects, including attending physicians, ward and clinic nurses, pharmacists, physician assistants, and relevant laboratory technicians.
5. Subject screening, consent, and enrollment.
6. Development of data collection worksheets as indicated.
7. Data collection and documentation.
8. Coordination of subject visits and follow-up.
9. Storage, dispensing, and accountability of the investigational product.
10. Collection and processing of laboratory samples.
11. Maintenance of subject and data confidentiality.
12. Organization and maintenance of study files and records.
13. Communication and collaboration with the trial sponsor, PI, monitor, IRB, and other site personnel.
14. Development of a system to track payments to the site based on budget milestones.
15. Coordination and/or administration of subject payments.

Many other tasks may be performed by the CRC depending on the specific needs of the study and the experience of the CRC.

subject follow-up, etc.) will result in accurate and complete subject data. A highly motivated staff can make this happen.

As noted earlier, CRCs may come from a variety of backgrounds, but most effective CRCs will share similar characteristics and work ethics. The following traits or qualities are common to many successful CRCs.

What Makes a Good Clinical Research Coordinator

1 *Attention to detail*. This is required in virtually all aspects of clinical trial work. Examples of detail work include performing protocol-required procedures and tests that must be completed in a designated manner at specific times, completing subject data forms, and dispensing the study product and completing accountability documents.

2 *Good communication skills*. CRCs interact with people of varied backgrounds and educational levels who are involved in all aspects of the trial, including sponsors, monitors, site study staff, laboratory personnel, study personnel at other sites, and subjects. The CRC must also communicate effectively with the PI throughout the study. Training skills and the ability to convey and generate enthusiasm when teaching other site personnel about the studies are also important.

3 *Flexibility*. A successful CRC moves quickly from one task to another and handles a workload that may change daily. The CRC may be completing paperwork to submit to the IRB on one day and conducting outpatient visits and processing blood samples for another study the next. The ability to oversee multiple tasks simultaneously and set priorities is important.

4 *Ability to work independently*. The investigator should clearly delineate the CRC's responsibilities and expectations. An effective CRC will be able to assimilate this information and function independently without the direct oversight of the PI.

5 *Organizational skills*. The CRC has many tasks to juggle; thus, the ability to manage numerous activities and work well under pressure is essential. There are many deadlines to meet, IRB submissions and data forms to complete, and tasks such as reporting SAEs, all of which must be done within specified timeframes.

Subinvestigators

When a trial requires a significant amount of physician time – for example, to recruit subjects and obtain informed consent, perform

physical assessments, or conduct outpatient visits – it may be helpful to identify persons who can function as subinvestigators. Subinvestigators must be listed in the investigator agreement or in section 6 on the Form FDA 1572 as individuals who will assist the PI in the conduct of the clinical trial. Subinvestigators are often colleagues or medical partners of the PI, or physicians completing specialty training at an institution. Subinvestigators must be completely familiar with the study – the protocol, study procedures, and reporting requirements – as well as with GCP. Subinvestigators usually assist with subject screening and recruitment, and often perform study-related procedures. While the PI may delegate some duties to subinvestigators, it remains the PI's responsibility to ensure that the study is conducted according to the protocol regardless of who performs study-specific activities.

Support Personnel

It is often important to have support personnel on the clinical trial team who can perform tasks such as photocopying, faxing, and scheduling appointments. This will allow all study personnel to make the best use of their time and skills. Communication with the support staff is important and expectations should be made clear before the trial begins.

Space and Resource Needs

An evaluation of the investigative site may reveal a need for additional space and resources in order to participate in clinical trials. Some of these resources will be necessary for all trials, while others may be study-specific. The following needs are common to most trials; therefore, the PI should plan to address these needs before starting a study.

Workspace for the Clinical Research Coordinator

A quiet workspace with a computer (with high-speed Internet access), a desk, and a telephone are essential for the CRC, who will need to make frequent telephone calls and complete a variety of data forms and other tasks. Ideally, the CRC's workspace has room for locked file cabinets (needed to store subject data forms and the site study file) and is near the location where study subjects will be

evaluated or treated, thereby allowing trial data forms and study reference materials to be readily available during subject visits. The CRC may also need access to appropriate space for meeting with study subjects and conducting follow-up visits.

Equipment

A computer and Internet access are necessary in most trials for communicating with the sponsor, coordinating center or laboratory facilities, and other study personnel. A computer may also be required for retrieving subject data and reports, and may be needed for electronically entering data collected during the study. In many studies, the Internet is used to disseminate and retrieve study materials as well as communicate through e-mail with sponsors and coordinating center personnel, making a computer and Internet access essential.

When electronic data capture (EDC) is used to record and submit data, it is critical to have high-speed Internet access; dial-up Internet access is not fast enough. Finding high-speed access can be an obstacle in some hospital settings. If high-speed Internet access is needed for the study but is not available, the PI should consider getting it installed or asking the sponsor to help support the cost of installation at the site.

In trials where refrigerators/freezers are required to store samples and specimens, it is important to make sure that the equipment meets the specifications established for the trial. The investigative team may need to be aware of the institution's backup system in case of power outage, when there is a need to maintain constant temperatures of refrigerated or frozen samples.

Access to photocopy and fax machines is a basic necessity. Every trial will require document photocopying and most require some forms to be faxed.

Storage Space

Storage space for subject data forms and study files will be needed. Depending on the trial and regulations specific to the country or region, subject study files may need to be kept for as long as 15 years. In trials where the test product is stored in the office of the CRC or the investigator rather than in the pharmacy, secured locked storage must be available. Only designated study-related personnel should have access to the test product, study records, and subject files.

Additional Space

Availability of a quiet work area is necessary for individuals monitoring the trial, to review subject and study records, and to meet with the CRC. A conference room or an unoccupied office can often be used for this purpose; however, the monitor should not be working in a room or office with access to files for other studies in which the site may be participating. The monitor will most likely need access to a telephone and computer with Internet access while at the investigative site.

The Local Institutional Review Board

Familiarity with the local IRB and its policies and procedures is key to the success of a clinical trial. Identify where and to whom the protocol and applicable study documents should be submitted, the frequency and time of IRB meetings, and the deadlines for submitting a protocol in order to ensure its review at the next scheduled meeting. The frequency with which IRBs meet varies, and can range from weekly to monthly and even bi-monthly or quarterly meetings. It may be necessary to submit the protocol and associated documents a week or more before the meeting, allowing IRB members adequate time to review the protocol. Many IRBs charge a fee for protocol review; the PI should check with the IRB to determine their policies and fees.

If there is not an IRB at the site, an external or independent IRB may be able to review clinical trial protocols. One of the challenges facing external IRBs located outside the community is fulfilling the regulatory requirement for "sensitivity to local factors." Local laws, institutional policies, professional and community standards, and population differences are all local factors that an IRB must consider when reviewing a protocol. A centralized review must allow for these important differences from one investigative site to another, based on the surrounding community and population.

Another option for obtaining IRB review of a protocol is to determine whether an IRB outside the PI's institution has unique expertise in the clinical area of study being investigated in the trial. The IRB of a large local hospital or tertiary care center may function in this role. This IRB may be willing to review protocols from nearby sites, with a representative from each site present at the meetings; this system helps overcome concerns about providing adequate consideration of local factors.

Examples of Local Factors

- A Catholic hospital may have a requirement that protocols and consent forms not make reference to birth control.
- The city of Seattle, Washington, requires that individuals participate in state counseling before enrolling in an AIDS trial.

The Central Institutional Review Board Initiative

Sponsored by the National Cancer Institute (NCI), a Central Institutional Review Board (CIRB) has been established for the review of adult and pediatric studies being conducted through NCI Cooperative Groups. The CIRB receives the study documents from the NCI Protocol Information Office and performs an initial review of the study. If the study is approved, the documents are posted on the Web site. Investigators who want to enroll subjects in the study can download the "Local IRB Facilitated Review Packet" and any other documents needed by their local IRB. The local IRB designates at least one voting member of the IRB to conduct the "facilitated review" of the study to determine whether there are local concerns that need to be addressed and whether to accept the CIRB Review. The CIRB conducts continuing reviews of studies and reviews of Serious Adverse Events (SAEs), Data Safety Monitoring Board (DSMB) reports, protocol amendments, national subject recruiting materials, etc. The local IRB is responsible for the review of local SAEs and the oversight of local conduct of the study.[5]

References

1 21 CFR 54.2(d)
2 http://www.hhs.gov/ohrp/humansubjects/finreltn/fguid.pdf
3 21CFR56.107(e)
4 Vogeli, C, Koski, G, Campbell, EG, Policies and Management of Conflicts of Interest Within Medical Research Institutional Review Boards: Results of a National Study. Acad Med. 2009 Apr; 84(4):488–494
5 http://www.ncicirb.org/

9 The Protocol

In this Chapter

Understanding the common components of a protocol:

- Objectives and endpoints
- Randomization types and methods
- Statistical considerations

"The beginning is the most important part of the work."

Plato (427 BC–347 BC), Greek author and philosopher

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

The *protocol* is a document that provides the background and framework for the planned study and describes how it will be implemented. Protocols are written by trial sponsor personnel, individual investigators, clinicians, scientists, or any combination of these individuals. Protocol authors often solicit input from prominent experts, practicing clinicians, and biostatisticians to ensure the protocol is clinically relevant and that the design is sufficiently statistically rigorous to meet its stated objectives; is practical for sites to enroll subjects; and can be completed in the proposed time frame. Many trials have a *Steering Committee* (a group of experts in the area of study) that is responsible for the oversight of a proposed trial or group of trials. Steering Committee members often contribute to protocol design, providing input on clinical issues, subject safety, and statistical matters.

Protocols can vary greatly in writing style, content, and flow; all, however, should provide the individual investigator with a thorough understanding of the goals of the study and the procedures involved. Depending on the written discussion of the background work and previous trials conducted, the complexity of the trial, required procedures, and many other factors, protocols may range in length from one or two pages to more than 100 pages, with 40–60 pages being a typical length.

In the United States, the trial sponsor submits the final protocol to the U.S. Food and Drug Administration (FDA) as part of an Investigational New Drug (IND) application or Investigational Device Exemption (IDE) application. The FDA must approve the protocol before the sponsor can initiate the clinical trial at the investigative sites. Not all protocols, however, require FDA review and approval. Protocols for clinical investigations of marketed drugs, protocols that are post-marketing (phase 4), and observational protocols (that is, there is no investigational product under study) do not need FDA approval before starting the trial; they do however require Institutional Review Board (IRB) approval.

Protocols for clinical investigations of marketed drugs do not require submission of an IND application if **all** of the following conditions are met:

1 Study data will not be reported to the FDA in support of a new indication for use or to support any other significant change in drug labeling.

2 The drug undergoing investigation is lawfully marketed as a prescription drug and the study data are not intended to support a significant change in the product advertising.

3 The study does not involve a change in the 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.

4 The study is conducted in compliance with the requirements for IRB review (21 CFR 56) and informed consent (21 CFR 50).

5 The study is conducted in compliance with the requirements concerning the promotion and sale of investigational drugs (21 CFR 312.7).

6 The study does not intend to invoke exception from informed consent requirements for emergency research (21 CFR 50.24).[1]

Regardless of whether FDA approval is required, investigators must submit the protocol to their IRB for review and approval. It is the role of the IRB to review the protocol in the context of the local patient population to determine whether the study design is scientifically valid, has an acceptable benefit-to-risk ratio for subjects, and the proposed subject selection is fair and equitable. The IRB also reviews the informed consent process and document, and seeks to ensure protection of subject privacy and data confidentiality. IRB approval must be granted before a clinical trial can be started at the investigative site.

If changes to a protocol for an IND or IDE study are indicated after initial FDA approval is obtained, the authors must write a protocol amendment and submit it to the FDA. IRBs must review and approve amendments before the changes to the protocol can be implemented. Once a protocol is finalized and approved, it becomes the final authority on enrollment criteria and

One example of **a study that did not require an IND application** is the BRIDGE (**B**ridging Anticoagulation in Patients who **R**equire Temporary **I**nterruption of Warfarin Therapy for an Elective Invasive Proce**D**ure or Sur**GE**ry) study. Warfarin is an oral anticoagulant commonly used to prevent stroke or thromboembolism in patients with chronic health conditions, such as atrial fibrillation, artificial heart valves, and previous venous or pulmonary thromboembolism. When patients on warfarin require surgery or other procedures, warfarin is typically stopped 5 days before the procedure or surgery to minimize the risk of bleeding.

The goal of the BRIDGE study is to compare bridging anticoagulation with "no bridging therapy" in patients with atrial fibrillation, and in doing so, establish a standard of care for patients who require temporary interruption of warfarin due to a procedure or elective surgery. To determine the risk of thromboembolus and bleeding complications, study subjects are randomized to receive either previously-marketed anticoagulants or placebo to bridge the time between pre- and postoperative warfarin therapy.

Because the study met all of the conditions in 21 CFR 312.2(b)(1), the protocol did not require an IND application or FDA approval, but did require informed consent of subjects and was registered with ClinicalTrials.gov, a government Web site that provides information about clinical trials.

Implementation of protocol-required procedures at the site

In some situations, site staffing or personnel issues dictate how study-required procedures will be implemented. For example, one site may have hospital laboratory personnel available to obtain protocol-required blood samples and perform the centrifuging, labeling, and freezing of the specimens, while at another site the Clinical Research Coordinator (CRC) may be responsible for performing these tasks. In other situations, logistical issues at the site may determine how protocol-related procedures are completed. For example, in a study where subjects are enrolled in the emergency department and must receive study drug within a short time after randomization, a hospital with a 24-hour pharmacy near the emergency department may store study drug in the pharmacy. However, an institution without a convenient pharmacy or 24-hour pharmacy staff may require study drug to be stored in a secure location within the emergency department.

Protocol Design Resources

A number of good protocol-design resources, including protocol templates, can be found online at the National Institutes of Health (NIH) Web site and at the Web site for Cancer Therapy Evaluation Program (CTEP), part of the National Cancer Institute (NCI). Several of the National Institutes have their own more specific protocol templates as well (e.g., the National Institute of Allergy and Infectious Diseases).[2] Please refer to Appendix E for protocol design resources.

Sample Table of Contents for a Protocol

Introduction
- Background
- Rationale
- Previous Animal/Human Studies

Objectives
- Endpoints

Trial Design
- Subject Selection
- Randomization
- Treatment Plan

Schedule of Assessments

Test Article
- Preparation, Packaging, and Labeling
- Dosing Schedule
- Storage, Dispensing, and Disposal/Return
- Accountability Records

Data Collection

Adverse Event Reporting

Statistical Analysis

Ethical Considerations
- Informed Consent
- Confidentiality
- Benefits/Risk of Harm
- Inclusion of Women, Children, and Minorities

Monitoring

Subject Compensation

Publication of Results

study procedures. While investigative sites may employ site-specific methods when implementing the study, specific eligibility criteria and study-required procedures must be followed carefully.

Common Components of a Protocol

Protocols come in many styles and sizes depending on the study phase, the type of product under investigation, and many other factors. In addition to collecting data to answer the primary research question(s), the protocol design must also ensure that regulatory requirements are met, including informed consent, reporting of adverse events (AEs), and protocol adherence.

Background and Rationale

The background section of the protocol includes results from pre-clinical studies and previous clinical trials. A description of the disease or disorder may be included and adequate information pertaining to safety and efficacy demonstrated in previous studies should be provided. The rationale for the study should clearly state the reason the trial is being conducted and should be consistent with the background information provided.

Study Organization

The organizational structure of the study is based on protocol needs, financial considerations, and logistical issues presented by the study design. Most protocols identify the groups and/or individuals who will manage various study activities, including site management, monitoring, safety reporting, test article distribution, and data

management. The use of central or core laboratory facilities should also be noted.

Objectives/Endpoints

The objectives of the study are often stated as primary and secondary endpoints (variables). Endpoints are measures believed to quantify the potential effect of a treatment or therapy under study. In addition to clinical endpoints, quality of life and economic factors may also be identified as endpoints.

A clinical endpoint should be:

1 Relevant and easy to interpret;
2 Clinically apparent and easy to identify; and
3 Sensitive to treatment differences.

Endpoints can be *single* or *composite*. A single primary endpoint might be undesirable in circumstances where clinically important events are rare and the treatment has an effect on a variety of important endpoints. Composite endpoints are commonly used in randomized controlled trials (RCTs) because they offer potential advantages, such as smaller sample sizes and shorter completion times. However, composite endpoints are also associated with certain risks, particularly if basic clinical and statistical requirements are not adequately respected. Difficulties in interpretation arise when the results of single components of the composite endpoint go in opposite directions, as well as when hard clinical outcomes are combined with soft endpoints, particularly if the latter occur much more frequently but are of lesser relevance. Accordingly, all individual components of the composite endpoints may require analysis using statistical techniques that use multiple testing and/or close testing procedures.

Examples of Endpoints

Single Endpoints

Death

Stroke

Rehospitalization

Quality of life parameters

Economic factors

Tumor regression/tumor size

Composite Endpoints

All-cause death or MI or stroke

All-cause death or hospitalization or cardiac arrest

All-cause death or end-stage renal disease or doubled serum creatinine

Quality of Life Parameters

The study of *quality* of life (QOL), in distinction to *quantity*, is in part, a consequence of the dramatically improved technology and other medical advancements that have prolonged life. In QOL studies, the effects of diseases on general health, physical functioning, emotional or psychological well-being, and social functioning over time are evaluated. In addition to important clinical questions regarding study treatments, QOL studies evaluate whether the treatments

Examples of Health-Related and Disease-Specific QOL Instruments

The **SF-36**, one of the most widely used instruments to measure health-related QOL, includes 36 questions covering 8 domains: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality, 6) social functioning, 7) role limitations due to emotional problems, and 8) mental health. It is available for multiple acute and chronic disorders, and is translated into 110 languages worldwide. Very importantly, it has reference data on normal populations to aid in understanding and interpreting scores both for clinical and research uses.[3]

The **DASI** (Duke Activity Status Index) is a measure of physical functioning, developed and validated in cardiac patients, that measures general health-related ability to perform 12 physical activities.[4]

The **WOMAC** (Western Ontario and McMaster University Osteoarthritis Index) instrument is a disease-specific measure of health status designed for use in osteoarthritis studies. It allows researchers to measure the intensity of pain and frustration of functional limitations related to arthritis.

The **FACT-G** (Functional Assessment of Cancer Therapy–General) instrument is a 27-item general questionnaire intended for use in patients with any type of cancer as well as a variety of other long-term illnesses such as HIV/AIDS and multiple sclerosis. The questions focus on physical well-being, social/family well-being, emotional well-being, and functional well-being. This tool is available in 30 languages and has several disease-, treatment-, and condition-specific subscales.

under investigation also have a positive impact on QOL by answering the following questions:

- Does the study treatment both extend and improve quality of life?
- Is the study treatment harmful to the subject's ability to function in daily life?

QOL data also help form our understanding of the primary outcomes for clinical practice and health policy. To better understand how illness affects day-to-day life, a number of validated instruments have been developed and used to evaluate quality of life based on subjects' perceptions of their ability to function. The SF-36, the DASI, the WOMAC, and the FACT-G are all examples of validated instruments.

Economic Factors

As interest in cost containment and health care reform continues to grow, issues that affect the short- and long-term cost of treatment become increasingly important. The economic impact of a treatment can be measured in terms of direct and indirect costs. Direct costs include the actual charges for hospitalization, treatment, drugs, medical supplies, and professional services; these are listed on a medical bill. Indirect costs, which are more difficult to measure, include such things as time away from work, loss of wages, and pain and suffering.

Surrogate Endpoints

In clinical trials, surrogate endpoints may be used instead of clinical outcomes. Surrogate endpoints are often physiological or biological markers that are thought to be highly correlated with the clinical endpoints for which they are substituting. Examples of surrogate markers in a cardiology trial might include LDL-C (low density lipoprotein cholesterol), CRP (C-reactive protein, a marker for inflammation), carotid intimal thickness, serum cholesterol levels, and myocardial infarct (heart attack) size. Surrogate markers may be used to substitute for an undesirable or rare primary endpoint. They may

also be used when there is a need for increased subject recruitment or lengthy follow-up or in circumstances where there is a shortage of resources needed to attain the required number of primary events in an event-driven trial.[5]

Surrogate endpoints may not have a one-to-one guaranteed relationship with the clinical outcome. Epidemiologic studies that demonstrate a statistical correlation between a biomarker and clinical outcome do not necessarily imply that modification of the biomarker will alter the natural history of the clinical outcome in question. The FDA has begun accepting evidence from trials that show a benefit to surrogate markers instead of endpoints; however, many believe that studies using surrogate endpoints should also be validated by conducting trials with hard clinical outcomes to be certain of the therapeutic effects postulated.

Study Design

Clinical research studies can be categorized into two groups: clinical treatment/intervention trials and observational studies. In treatment/intervention studies, researchers evaluate the effects of the treatment on a select group of subjects, while in observational studies, researchers observe and collect data without intervening in the course of events. Studies can also be *prospective*, collecting data from the time of the study forward, or *retrospective*, where data from past events is collected. The focus of this book is prospective clinical treatment/intervention trials, but a brief description of observational studies can be found later in this chapter.

The design of a clinical trial functions as the framework by which the objectives will be met. Many factors are considered when determining the design for a given trial, including the use of control groups, randomization strategies, and whether a trial can or should be blinded to investigators and/or study subjects. While not appropriate for all research questions or practical in all settings, randomized, double-blind, placebo-controlled trials are considered the "gold standard" of clinical trial design.

Are Surrogate Endpoints Reliable?

Use of reduction in ventricular ectopic contractions as a surrogate for decreased cardiovascular-related mortality provides a classic example of the unreliability of surrogate endpoints. Ventricular arrhythmia is associated with an almost fourfold increase in the risk for death related to cardiac complications, particularly sudden death. It was hypothesized that suppression of ventricular arrhythmias after myocardial infarction would reduce the rate of death. Three new drugs (encainide, flecainide, and moricizine) were found to suppress arrhythmias effectively and were approved by the FDA for use in patients with life-threatening or severely symptomatic arrhythmias. Although follow-up trials had not been done to determine whether the reduction in arrhythmias would lead to a reduction in death rates, more than 200,000 persons per year eventually took these drugs in the United States. The Cardiac Arrhythmia Suppression Trial (CAST) evaluated how the three drugs would affect survival of patients who had had myocardial infarction and had at least 10 premature ventricular beats per hour. The early results from CAST were startling.[6] The encainide and flecainide arms of the trial were terminated early when 33 sudden deaths occurred in patients taking either drug compared with only 9 in the matching placebo group. A total of 56 patients in the encainide and flecainide group died, and 22 patients in the placebo group died. After the data were fully analyzed, the sudden death comparison was 43 and 16 and the number of deaths was 63 in the encainide and flecainide group and 26 in the placebo group.[7] Later results from CAST also established an increased risk for death in patients receiving moricizine.[8]

Beneficence

The second principle described in the Belmont Report – *beneficence*, or the obligation to do no harm, to maximize benefits and minimize potential risk of harm – requires a careful evaluation of the potential risk-benefit ratio as part of designing the study and its protocol. The Belmont Report states that justifiable research should be evaluated in part based on the assessment of a study design that reduces risks to only those that are necessary to achieve the research objective, including whether it is even necessary to use human subjects; in addition, the use of vulnerable subjects must be justified. Refer to the Belmont Report for further discussion of beneficence in study design.

Declaration of Helsinki Statement on Placebo Use

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

(Declaration of Helsinki, Last amended at the WMA General Assembly, Seoul, October 2008)

Use of Control Groups

When the makeup of the groups of subjects being evaluated is controlled, it creates more homogenous groups for comparison. Thus investigators can conclude that differences in the groups are related to the treatment under investigation, rather than to differences within the groups of subjects. Examples of types of controls include use of placebo (inert substance), use of active medication, a current device, or standard care (known as an *active control*), no treatment, or administration of a different dose of the same medicine (sometimes called a *dose-ranging study*).

Placebo Control

The use of placebo is appropriate in clinical trials where no standard treatment exists and there is clinical *equipoise*; that is, there is no consensus among health care experts regarding the best treatment. While subjects randomly assigned to active treatment may receive benefit from a test product, there is also the possibility that subjects assigned to placebo will avoid side effects or toxicities of a potentially harmful or ineffective test product. When standard treatment exists and there is consensus among health care experts regarding the effectiveness of standard treatment, the test product should be compared to the standard treatment rather than placebo, as withholding a treatment known to be safe and effective is considered unethical in most circumstances.

Sham Procedures

In a small number of procedure/device trials, subjects are randomized to a "sham" procedure to reduce the chance of subject bias, especially when assessing subjective endpoints such as subject-reported symptoms (e.g., pain). One example of a sham procedure can be found in an arthroscopic surgery trial conducted on subjects with osteoarthritis of the knee. Under local anesthesia, subjects in the placebo arm had a small incision made in the knee but the arthroscope was not actually inserted. To maintain the blind for subjects, the surgeons verbally requested the same surgical instruments and manipulated the knees of subjects just as they would have if performing

the real arthroscopic procedure. Pain and function were assessed at intervals over a 24-month follow-up period.[9] A second example of a sham procedure involves the use of acupuncture. In order to evaluate the effects of acupuncture in a clinical trial, a sham needle that does not actually penetrate the skin has been developed and tested to create the sensation of inserting acupuncture needles in subjects randomly assigned to a control arm with no acupuncture.[10]

Randomization

Randomization is the technique of assigning subjects to treatment groups without bias by establishing a plan for allocation to treatment groups before study initiation. Through the use of randomization, the subject has a known chance (for example, one chance in two, which is a 1:1 chance, or equal chance; or one chance in three, which is a 1:2 chance) of being given a particular treatment option, but the choice of treatment is not made by the investigator or subject and cannot be predicted. The goal of randomization is to produce treatment groups that are as similar as possible, so that the differences seen in subject outcomes reflect the effect of the treatment rather than differences in the treatment groups themselves. Since none of the treatment groups are known to be superior at the onset of the trial, randomization is an ethical approach to assigning treatment.

In spite of the implied meaning of the term "random," there is usually nothing random or arbitrary about the planning and strategies used in determining the type of randomization employed in a study. The randomization scheme is typically developed by a statistician, taking into account all the relevant aspects of the study design.

Randomized Controlled Trial

A randomized controlled trial uses randomization to minimize bias in assigning treatment to subjects. While some subjects are randomly assigned to receive the investigational treatment, other subjects (control group) are assigned to standard treatment or non-treatment (standard therapy or placebo).

Cross-Over Trial

In a cross-over trial, subjects get both study treatments (or treatment and placebo), one after the other. Ideally, subjects are randomized to a specific treatment order, with some subjects getting treatment "A" first, followed by "B," while other subjects receive treatment "B" first, followed by treatment "A." Each subject serves as his or her own control.

Early Use of Randomization

Randomized scientific studies were first introduced by the pioneering statistician and geneticist Sir Ronald Aylmer Fisher, who applied the technique to a series of agricultural field studies in Britain in the 1920s.[11] When first used in human subjects in the early 1930s, randomization was accomplished by literally tossing a coin to determine the treatment group assignment. Current methods of randomization vary widely depending on trial design, but include simple randomization (subjects assigned treatment based on a code – often by order of admission into the study), block randomization (subjects proportionately assigned to treatment groups within a pre-specified number or "block" of subjects), and stratification (subjects assigned to treatment groups based on sex, age, weight, intensity of disease, or other relevant prognostic variables expected to affect outcome).

Randomization

Although the results of a repeated random event such as the outcome of a coin toss *average out* to a 1:1 chance of getting either heads or tails in the long term, it is quite possible to experience a string of repeated outcomes in the short term. Thus, while flipping a coin 1000 times will usually result in roughly half the coin flips being heads and half being tails, it sometimes happens that a person flipping a coin might get, for instance, 20 tails in a row. This means that if a study with a relatively small number of subjects uses a simple randomization process analogous to a coin toss, a string of "heads" or "tails" could cause the arms of the study to become unbalanced. This can ultimately affect the analysis, which is usually planned under the assumption that a certain number of subjects will be randomly assigned to each arm.

Statisticians can avoid this problem by using a mode of randomization (sometimes called *dynamic allocation* or a *minimization algorithm*) that takes into account previous randomizations. In such a case, if there has been a string of randomizations that have all been to the same arm of the study, the statistical "coin" becomes "weighted" so that for a while, the chances of getting the other result will be not 1:1, but perhaps 2:1, or 3:1. This "weighting" can be kept in place until the study arms become balanced, at which point the weight of the coin becomes 1:1 again, until another imbalance occurs. Other methods to prevent randomization imbalances can be used as well, such as *block randomizations*.

Types of Randomization

The plan for performing the randomization should be clearly described in the protocol. There are many methods of randomization, including *simple randomization*, where randomization results are similar to treatment assignment based on a coin toss, but may be very imbalanced if the sample size is small. *Block randomization* is done through small groups, or blocks, of subjects who are randomized to a treatment strategy, resulting in a close balance of treatment strategies at all times. The block size is not known to anyone other than the unblinded statistician and is kept secret until the study is completed. In order to minimize the differences of important characteristics between treatment groups, *stratified randomization* may be used to randomize treatment assignments in subgroups of subjects. For example, subgroups are commonly based on age, sex, or the clinical center where the subject is enrolled. *Permuted block randomization* adds an additional element of blinding by varying the number of subjects in the blocks. Therefore, instead of every block being made up of 4 subjects, for example, with two subjects receiving Treatment A and two subjects receiving Treatment B, the blocks would be made up of varying numbers of subjects, such as 6 subjects or 8 subjects. Careful consideration must be given to the block size (small versus large), number of varying blocks, and avoidance of block sizes being multiples of each other based on number of subjects required, trial design and the extent of stratification to ensure treatment balance. If a trial stops mid-block, random permuted blocks can result in treatment imbalance. Sophisticated statistical methods can be applied as restrictions to the random permuted block randomization design to avoid severe treatment imbalances while still providing unbiased estimators of treatment differences. The smaller the block size, the more often balance is forced. For example, in an open-label unblinded study randomizing 100 subjects with blocks of 2 subjects; it is easy to know every second participant's assignment in advance. This would obviously lead to a high selection bias.

Methods of Randomization

Methods of randomization have changed over time as new techniques and technologies become available. Early randomization was performed by opening numbered sealed envelopes placed at each site. This method was prone to problems because envelopes could be opened out-of-order

or someone could easily tamper with the envelopes. Central randomization is currently the most prevalent method, and is done either by telephone or via the Internet. One common form of central randomization is the *interactive voice response system (IVRS)*, in which the caller, usually a physician, nurse, or clinical research coordinator, follows a series of prompts to activate a randomization for a particular subject. IVRS is an attractive option because it provides quick access to randomization, as well as an automatic recording of pertinent eligibility criteria and/or subject characteristics at the time of study enrollment.

Blinding

Blinding (occasionally referred to as *masking*) is another technique used to avoid introducing bias in a clinical trial. Several types of blinding used in clinical trials are listed below:

A *single-blind* study is one in which the intervention is unknown to the subject (the subject is "blind" to the treatment). Blinding the subject to treatment reduces the potential for the "placebo effect," which can occur when a subject has an *expectation* of a benefit from study treatment (rather than receiving benefit from the actual treatment itself). The placebo effect, which can be particularly troublesome for studies assessing subjective outcomes such as pain or QOL factors, is less likely to occur if the subject is blinded to the treatment.

To prevent investigators and study staff from consciously or unconsciously introducing bias into the study, study drug may be double-blinded. A *double-blind* study is one in which both the study participants and those administering the study drug (the investigator and study staff) are "blinded" to the treatment being given.

Double-dummy is a technique used to maintain the blind when two treatments cannot be manufactured to appear identical, such as when an oral therapy is being compared against an intravenous therapy. Supplies are prepared for "treatment A" (active drug A and identical placebo A) and for "treatment B" (active drug B and identical placebo B). Subjects are assigned to a treatment strategy of one from each treatment set of drugs – either active drug A and placebo B or active drug B and placebo A.

Blinding, however, may not always be feasible. In some studies, it may be impossible to blind the persons who administer a medicine or treatment (for example, giving a nebulized treatment versus chest percussion therapy), or when subjects are randomized to device implantation versus no device and a sham procedure is not possible.

Use of Blinding to Test Animal Magnetism

Franz Mesmer, a German physician born in 1734, developed the theory of "animal magnetism," believing that humans could manipulate their health and cure diseases using magnetic force. When the medical community tried to bring charges of fraud against Mesmer, he left Austria and set up practice in France where he continued to advocate his theory. Mesmer believed that illness occurred when there was a blockage of an invisible body fluid present throughout the universe. He claimed that he could eliminate the blockage and restore health by pointing his finger toward the subject's head, inducing a trance-like state by staring into their eyes, thus "mesmerizing" the subject. Sometimes his treatment led to a "crisis" where the subject would have symptoms such as seizures, hiccoughs, or uncontrollable laughter that, according to Mesmer, forced the body fluid back into proper flow, restoring health.

When news of this treatment and the skepticism surrounding its veracity reached King Louis XVI of France in 1784, he appointed a commission of leading scientists, including Benjamin Franklin, to examine and evaluate animal magnetism. The commissioners observed that subjects who were told they were being treated with "magnetized" water subsequently experienced a crisis. However, when subjects were blindfolded and told they were being treated with magnetized water, when in fact they were not, they still experienced a crisis. The reverse was also true – subjects who unknowingly drank or were exposed to "magnetized" water had no response and remained unaffected.

Thus, through the use of blinding, the commission determined that it was human imagination rather than animal magnetism that led to the crises and health restoration. The commissioners concluded that subjects who were hopeful for recovery believed that treatment administered with authority would lead to an improvement in health or cure.[12]

Unblinding

Unblinding of study treatment can seriously affect the integrity of the study and is strongly discouraged unless knowledge of the study assignment is imperative to determine the appropriate treatment for unexpected or serious adverse events. When unblinding is necessary to ensure the safety of a research subject, unblinding should be performed according to the process described in the protocol. The decision to unblind often involves a discussion between the site investigator and the medical monitor at the sponsor.

Observational Studies

A number of observational studies are conducted to observe and gain information rather than test a treatment or intervention. Observational studies are therefore not clinical trials as such, but are considered clinical research. Observational studies include cohort studies, case-control studies, cross-sectional studies, and longitudinal studies.

Cohort Study

A cohort study is often (but not always) prospective (also called *concurrent*) and follows a group that does not exhibit the condition

or outcome of interest at the start of the study. After a specified amount of time elapses, comparisons are made *within* the cohort between persons who develop the outcome and those who do not. Retrospective (or *nonconcurrent*) cohort studies can be done, but require careful blinding procedures on the part of the investigators.[13]

One very well known cohort study, which began in 1948, is the Framingham Heart Study, conducted by the National Heart, Lung, and Blood Institute (NHLBI), one of the National Institutes of Health. The objective of this study was to identify common characteristics that contribute to cardiovascular disease, the leading cause of death in the United States. Initially, 5209 men and women between the ages of 30 and 62 who lived in Framingham, Massachusetts, underwent physical and lifestyle examinations, followed by re-examination every 2 years. In 1971, a second-generation group of 5124 subjects were enrolled. These subjects were the original participants' adult children and their spouses. A third generation (the grandchildren of the original subjects) is currently being evaluated.[14]

Framingham Heart Study: Significant Findings

1960	Cigarette smoking found to increase the risk of heart disease
1961	Cholesterol level, blood pressure, and electrocardiogram abnormalities found to increase the risk of heart disease
1967	Physical activity found to reduce the risk of heart disease and obesity to increase the risk of heart disease
1970	High blood pressure found to increase the risk of stroke
1976	Menopause found to increase the risk of heart disease
1978	Psychosocial factors found to affect heart disease
1988	High levels of HDL cholesterol found to reduce risk of death
1996	Progression from hypertension to heart failure described
1999	Lifetime risk at age 40 years of developing coronary heart disease is one in two for men and one in three for women
2001	High-normal blood pressure is associated with an increased risk of cardiovascular disease, emphasizing the need to determine whether lowering high-normal blood pressure can reduce the risk of cardiovascular disease
2002	Lifetime risk of developing high blood pressure in middle-aged adults is 9 in 10
2002	Obesity is a risk factor for heart failure
2005	Lifetime risk of becoming overweight exceeds 70 percent; lifetime risk for obesity approximates 1 in 2
2006	NHLBI announces a new genome-wide association study at the Framingham Heart Study in collaboration with Boston University School of Medicine to be known as the SHARe project (SNP Health Association Resource)[15]

Sir Richard Doll: Cigarette Smoking Causes Lung Cancer

Sir Richard Doll was a distinguished epidemiologist working at the Medical Research Council (MRC) in London, England, in 1948, when government statisticians raised awareness of a recent increase in lung cancer deaths. The MRC wanted to determine if the increase was real and whether a cause could be identified. At the time, smoking seemed a normal and harmless habit; Doll and others thought the most likely cause of the lung cancer increase was pollution from coal fires, tarring of roads, and car exhaust. Doll and associates interviewed 650 male patients with suspected lung, liver, or bowel cancer in London hospitals. They also interviewed hospital patients with other diagnoses. The results were compelling and clear: those who were diagnosed with lung cancers were smokers and those who did not have lung cancer were non-smokers.[17]

MURDOCK Longitudinal Study

The *Measurement to Understand Reclassification of Disease Of Cabarrus/Kannapolis* (MURDOCK Study) is dedicated to building a biorepository (or database) of patient clinical data matched with biological samples, such as blood, from 50,000 local participants in Kannapolis and in Cabarrus County, North Carolina. This longitudinal study that began in February 2007 will serve as a valuable tool for defining – at a molecular level – diseases that are threatening to cripple our society.[19]

Case-Control Study

Case-control studies are usually retrospective and match persons known to have a condition or outcome with those who do not. Case-control studies are particularly sensitive to a variety of confounding issues, including the method used to match cases with controls, selection bias with regard to the population, and recall bias.[16]

One well-known case-control study was conducted by Sir Richard Doll, an epidemiologist who demonstrated the causative link between cigarette smoking and lung cancer.

Cross-Sectional Study

A cross-sectional study provides a "snapshot" of the disease characteristics in a defined population at a specific point in time. For example, one cross-sectional study, the National Health and Nutrition Examination Survey, looked at the prevalence of overweight and obese individuals in the United States. Researchers studied children between the ages of 2 and 19 years of age, and adults 20 years and older, to determine the prevalence of overweight children and obese adults. This study concluded that the prevalence of overweight children and obese men increased significantly from 1999 to 2004 while there was no overall increase in obesity in women in the same time period.[18] Cross-sectional studies can be used to investigate whether certain variables or outcomes are associated with each other, but cannot be used to establish whether the relationship is a causal one.

Longitudinal Study

A study that looks at subjects at various points over time is referred to as a longitudinal study; this is in contrast to a cross-sectional study that looks only at a single point in time. Many studies are longitudinal, including cohort and some case-control studies that follow subjects over a designated period of time.

Study Population

The third principle in the Belmont Report is *justic*e, which is applied through the fair and equitable selection of study subjects. Social fairness requires that subjects are identified

based on objective criteria and not whether a subject is considered "desirable" according to social criteria (such as being employed, or belonging to a particular race or socioeconomic group) and enrolled in a trial likely to provide benefit; or "undesirable" and therefore enrolled in a more risky trial. There is an order of preference in the selection of classes of subjects; for example, one should enroll adults before children and non-vulnerable subjects before vulnerable subjects. However, fair subject selection may also require the inclusion of certain groups, such as women, children, and minorities so that trial results can be accurately applied ("generalized") to these groups of individuals. The principle of justice also requires that study subjects be among the possible beneficiaries of the research. The application of this aspect of justice can present problems in a number of situations, particularly when the testing of new products is done in communities or countries where it is unlikely that subjects will have access to an approved marketed product (e.g., testing a new vaccine for AIDS in a country where the cost of the marketed vaccine would prohibit its use). All clinical protocols should identify the study population with the principle of justice in mind.

The protocol should describe the target population in terms of eligibility, which is divided into inclusion and exclusion criteria. These criteria typically relate to characteristics of subjects to be enrolled, characteristics of the disease and treatment, the results of screening tests, and other factors. Eligibility criteria often refer to subject age, pre-existing history and conditions, reproductive capability, and screening laboratory values in addition to the specific disease or condition being treated.

The protocol usually identifies how many subjects will be enrolled over a specific period of time, and may note the number of sites and countries participating in the study. As a general rule, subjects should not participate in more than one trial at a time; however, there are exceptions to this. The protocol should identify whether subjects may participate in concurrent studies or specify the time period that must elapse since last participating in another trial.

Common Eligibility Requirements: Inclusion and Exclusion Criteria

Subject Characteristics: sex; age; weight; pregnancy; use/abuse of tobacco, alcohol, and drugs; surgical history; allergies/sensitivities

Disease and Treatment Characteristics: disease being studied; use of concomitant medications; history of other diseases and hospitalizations; current clinical status

Screening Tests: results of tests or evaluations that would include or exclude a subject from participating

Other Factors: participation in another clinical trial, ability of subject to fully cooperate, geographic location[20]

Study Treatment Plan

The protocol should clearly delineate the activities to be performed in the implementation of the study. This includes a plan for administration of the study treatment and a list of the assessments and procedures that should be performed throughout the duration of

Figure 9.1 Sample Schedule of Assessments

Schedule of Assessments						
	Screening/ Baseline	**30-Day**	**90-Day**	**Major/Minor Bleeding**	**(Re)MI or Recurrent Ischemia**	**2 Weeks After Study Drug Stopped**
ECG (12-lead)	X				X	X
Vital signs/weight	X					X
Serum pregnancy test	X					
CK-MB and troponin	X				X	
PLT count/Hgb/Hct	X	X	X	X		X
Serum creatinine	X	X	X	X	X	X
WBC, SGPT total bilirubin	X	X	X			X

the study. Protocols often include a *Schedule of Assessments*, a chart that lists all study-required assessments and the timepoints at which they should be performed. Required assessments will vary widely depending on the treatment and type of study, and may include laboratory samples, tests, procedures, examinations, and questionnaires.

Safety Assessment, Management, and Reporting

While some safety concerns may be anticipated based on previous studies or the investigational treatment's mechanism of action, the protocol should specify how all safety issues, both expected and unexpected, should be handled. Management of adverse events and reporting requirements should be provided, including the requirements and process for the expedited reporting of events.

Criteria for making changes in the proposed study treatment plan, such as study drug dose increases or reductions, termination, or early withdrawal, should be described in the protocol.

Replacement of Withdrawn, Dropped Out, and Lost to Follow-up Subjects

The protocol should specify how to manage situations when subjects withdraw or drop out for any reason. Some studies require the replacement of subjects and will specify how replacement subjects should be assigned study treatment, while other studies do not allow the replacement of subjects. Subjects who have been withdrawn by the investigator for safety reasons may need to have follow-up visits conducted, and subjects who have withdrawn consent may be willing to continue some of the protocol-required follow-up procedures or tests. The protocol should indicate how the data for these subjects will be included in the analysis. The protocol may also specify the methods that should be taken to try to locate lost to follow-up subjects.

Statistical Aspects

The role of statistics in designing a study and analyzing the results is critically important. The trial must be designed to allow appropriate analysis and interpretation of the data. Some statistical considerations are listed below:

Power

Power represents the ability to detect a statistical difference between treatments when a difference actually exists. Typically, trials are powered to provide at least an 80% chance of detecting a difference.

Sample Size

Sample size refers to the number of subjects needed to participate in a given trial; the sample size must be sufficient to detect the effects of the treatment(s) under investigation in the target population. The number of study subjects should be large enough to provide a reliable answer to the questions being addressed in the protocol and is usually determined by the primary objective(s) of the study. Statistical formulae are used to calculate the number of subjects needed to attain a prespecified event rate or treatment difference. Other issues, such as subjects who are lost to follow-up or non-compliant, or who withdraw consent before study completion must be considered when determining adequate sample size.

Trial statisticians make sample size calculations based on the:

1 Magnitude of the expected or desired effect;
2 Variability (may be estimated) of the events or endpoints being analyzed; and
3 Desired probability (power) to see the effect with a defined significance level – usually a power of 80% or greater.

Sample size adjustment may occur in long-term trials when there is an opportunity to check the assumptions upon which the initial sample size calculation was based. An adaptive trial design, such as one that is event-driven, involves ongoing assessment of the sample size to avoid under- or over-allotment of subjects. In an event-driven trial, initial assumptions regarding the anticipated occurrence of endpoint events are used to calculate the appropriate number of subjects. To allow for subjects who withdraw or who are lost to follow-up, an additional increase (e.g., 10%) in the number of subjects may be added to ensure adequate enrollment in all treatment arms. Decisions to extend the duration of the enrollment and treatment period or increase the sample size are based on the interim review.

An interim check on blinded data may reveal that overall response variances, event rates, or survival are not as anticipated. The sample size may then be increased or decreased as necessary based on these factors. A sample size adjustment should either be specified in the original protocol study design or included in a protocol amendment.

Intention-to-treat Principle

The intention-to-treat (or "intent-to-treat") (ITT) principle is a standard method for analyzing data in clinical trials. This principle is based on the idea that treatment effect is best assessed when analyzed as part of the group to which the subject was randomized (intended), no matter what treatment the subject actually received. This means that if a subject received a treatment different from the one to which he or she was randomized, the data will be analyzed as if the subject received the originally intended treatment. Although the advantages of this principle may not be intuitively obvious, years of theoretical and practical work have demonstrated that ITT analysis prevents biases from influencing the interpretation of a clinical trial's outcomes.

Before this principle was widely accepted, subjects were excluded from analyses for many reasons. Some of the reasons were:

1 Subjects were later found to not have met eligibility criteria.
2 Subjects "crossed over" to receive a different treatment assignment, or were incorrectly given a treatment other than the assigned treatment.
3 Subjects were noncompliant with study treatment.
4 Subjects dropped out of the study before completing the full course of study therapy.

While excluding these subjects from efficacy analyses may seem reasonable, it often leads to excluding a large number of enrolled

subjects. Exclusion of these subjects opposes the purpose of the study – to evaluate the treatment under investigation in subjects suspected of meeting the criteria for the target population. In reality, practicing clinicians treat subjects prospectively, often based on the disease or condition the subject is suspected of having. Therefore, when analyzing data using the ITT principle and including all enrolled subjects, study findings will more closely resemble the results seen in clinical practice.

Most major trials use ITT methodology, although additional analyses evaluating only those subjects who received treatment may also be performed. Therefore investigators must be comfortable with all treatment strategies used in a trial and every effort must be made to administer the assigned treatment and ensure that subjects receive the full course of study therapy.

Interim Analysis

An *interim analysis* is performed at any time before the final data analysis, usually to evaluate treatment differences, efficacy, and significant safety issues in phase 2b and phase 3 trials. Interim analyses may be performed for a number of reasons. Ethical and scientific reasons relate to ensuring that a superior treatment is not withheld from subjects longer than necessary; financial concerns relate to the high cost of trials and the expense of continuing a trial that cannot demonstrate significant treatment differences; practical considerations relate to ensuring that a trial is progressing as planned.

The purpose and timing of planned interim analyses must be stated in the protocol. One or more analyses may be specified at designated timepoints during the course of a study. The timing of the interim analyses may be based on enrollment (such as when half of the subjects are enrolled), or based on a period of time (for example, 6 months into a year-long enrollment period). The timing and number of interim analyses will vary depending on the study, but they are usually planned to represent a cross-section of the total enrollment. Since an unplanned interim analysis may introduce a flaw into a study and weaken the confidence in study conclusion, the plan for interim analyses must be carefully thought out and clearly specified in the protocol.

Example of How the Intention-to-Treat Principle Might Be Applied

A blinded trial is being conducted to compare heparin to an investigational anticoagulant in subjects having an acute myocardial infarction (heart attack). An acutely ill subject is randomly assigned to double-blind study treatment (heparin or investigational anticoagulant). However, after randomization, the clinician decides to give open-label heparin instead of blinded study drug so as to be sure of what treatment the subject is receiving. If the data are analyzed according to actual treatment administered, there would be potential for the group of subjects receiving heparin to include more high-risk subjects, resulting in a bias toward higher mortality in the heparin group. However, if the analysis is performed based on the ITT principle, the data would be analyzed according to randomization assignment rather than on actual treatment administered. This keeps the treatment groups similar and reduces this type of bias.

Subjects cannot be denied known life-saving or life-extending treatment

In the first clinical study of the AIDS drug zidovudine (AZT), a clear survival advantage for subjects receiving zidovudine was seen well before the trial was scheduled to end. The trial was ended early and within a week, the FDA authorized a protocol allowing more than 4000 subjects to receive zidovudine before it was approved for marketing under the brand name Retrovir.

Figure 9.2 Examples of Interim Analysis Findings and Resulting Outcomes or Actions

Examples of Interim Analysis Findings and Resulting Outcomes or Actions	
Finding	**Outcome or Action**
No significant difference or safety concerns in treatment groups	Continue study as planned
Unequivocal positive effect in one of the treatment groups	Stop study so that all subjects can be offered superior treatment
Serious safety concerns with one or more treatment group	Stop or modify study
Lower-than-expected event rate	Increase the number of subjects to be enrolled

The timing and criteria for analysis should be documented, as should guidelines for early termination of the study.

The interim data analysis is performed by a statistician who provides the information to members of a Data and Safety Monitoring Board. Since an interim analysis may require unblinding of treatment group assignments, it should be a completely confidential process. All data presented and reviewed during interim analyses should remain confidential until enrollment has stopped and the trial is unblinded.

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) is an independent committee of clinicians, statisticians, ethicists, and other specialists who are knowledgeable in the area of study. The role of the committee is to assess the progress of a trial, its safety, and/or its efficacy at intervals specified in the protocol. This committee is established by the sponsor; the committee membership and responsibilities should be described in the protocol. Typically, the members of the committee have no involvement in the study or any financial links to the treatment(s) under study. This is intended to maintain confidentiality and protect the integrity of the data, ensuring a fair and unbiased review. However, in some phase 2 trials, DSMBs may include representatives from the study sponsor because of their knowledge of the study treatment.

The DSMB is provided with confidential data during the course of the trial. The committee may recommend that a study be continued,

modified, or stopped based on the data provided at the time of an interim analysis.

Other names for this committee include a Safety and Efficacy Monitoring Committee (SEMC), Data and Safety Monitoring Committee (DSMC), and Data Monitoring Committee (DMC).

Subject Data and Record Retention

The protocol may identify subject data that will be collected and provide a timeline for data submission. The length of time for record retention should be indicated; when study sponsors require record retention for a longer period than specified in the regulations, this should be noted. The protocol should also provide the name of persons to contact before destroying study records at the end of the record retention period.

Monitoring

Monitoring is performed in clinical research to oversee the quality of the trial and the study conduct at the sites where subjects are enrolled and treated. Site monitoring typically includes a determination of protocol adherence and source document verification to confirm the accuracy of the data being submitted. The protocol may identify the monitoring plan and may outline the frequency of monitoring visits, the percentage of data forms to be monitored, and the group responsible for the monitoring activities, as well as other aspects of monitoring.

References

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Investigator Responsibilities for Record Retention

21 CFR. 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 such as 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.

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10 Study Feasibility: Reviewing a Specific Protocol

In this Chapter

- Using the protocol to determine if a trial is right for your site
- Creating a trial budget for your site

"For knowledge, too, is itself power."

Francis Bacon (1561–1626), English philosopher and statesman; father of modern scientific method

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

A protocol provides the understanding and the framework for a clinical trial. The author of a protocol usually seeks input from various persons who contribute expertise toward the development of a well-written, well–thought-out protocol. Once a protocol is written, some institutions have established committees to perform a pre-review to ensure scientific quality before the protocol can be submitted to the Institutional Review Board (IRB).

A pharmaceutical company or a colleague in your own institution or elsewhere may approach you with a developed protocol to ask if you would like to be an investigator in the study. Unless you have been involved in the process of developing or finalizing the protocol, you will be provided a nearly-final draft or an FDA-approved protocol to review, with the study design and analysis plan already established. Once you receive the protocol, you should consider all aspects of the study to determine whether you can – or want to – be an investigator. You must decide whether the goals and design of the protocol fit within the scope of your clinical practice, whether you have sufficient access to the target patient population to be able to recruit appropriate subjects, and whether you have the time and resources to conduct the study.

Reviewing a Specific Protocol

- Will the study design work in your institution?
- Do you have access to the appropriate subject population?
- Do you have the time needed to complete the protocol requirements?
- Do you have sufficient study personnel to perform the trial-related activities?
- Are there special procedures or laboratory requirements that would be difficult to perform at your institution?
- Is funding sufficient to cover costs of conducting the study at your site?

Reviewing a Specific Protocol

You should carefully review and evaluate how the protocol differs from your routine clinical practice, determine whether the appropriate subject population and resources are available at your institution, and identify whether any requirements unique to the protocol can be met at your site.

The following questions will help you determine if participation in a particular study is right for your institution.

Study Design

What type of study is outlined in the protocol? For example, studies may be performed at only one site or at many sites (multi-center). Study drug may be open-label, single-blind, or double-blind with a placebo-control group. The study may require "sham" procedures to be performed to maintain the study blind, or may require years of follow-up for a longitudinal study. In addition to identifying the type of study, consider the following:

1 How do the protocol requirements compare to the routine standard of care for this patient population?

2 Are there non-routine tests or procedures that need to be performed?

3 How long will study enrollment and follow-up last?

4 How will study drug dosing be determined?

5 Are outpatient visits required? If so, how many?

6 Is the study endpoint-driven, rather than based on a specific number of subjects to be enrolled? Endpoint-driven trials may take longer than planned to achieve the designated number of endpoints, increasing the amount of time required for study completion.

Research Subject Population

To determine whether prospective subjects are eligible for study enrollment, an initial screening must be done. Screening may range from reviewing the medical history and laboratory results of potential subjects to performing invasive procedures. What is the target subject population specified in the protocol? Does your practice or institution see enough patients with the target disease or condition? Depending on protocol eligibility criteria, it may be that only a small portion of the patients with the target disease are eligible for enrollment.

1 What are the eligibility criteria? Are they realistic for the disease under study and broad enough to allow enrollment of a sufficient number of subjects?

2 How many subjects are you expected to enroll, and over what time period?

3 Are risks to subjects minimized and reasonable in relation to the potential benefits?

4 How many prospective subjects do you anticipate will need to be screened to enroll the required number of subjects? When, where, and by whom will screening be done?

5 Will your physician colleagues participate in the screening of prospective subjects, thereby contributing to the number of subjects enrolled at the site?

6 Is the protocol diagnosis a seasonal condition (e.g., asthma, allergic rhinitis) that will limit the time, number, or frequency of subjects seeking medical care at the time the study is being conducted?

7 Are there competing clinical trials that target the same population?

Investigator Time Requirements

It is important to quantify the amount of time you will need to allocate for overseeing subject safety and study-related staff activities, and to perform all study activities within the regulatory requirements and standards of good clinical practice.

1 Is there a "start-up" meeting (often called an Investigator Meeting) that the Principal Investigator (PI) and Clinical Research Coordinator (CRC) should attend? How long does the meeting last? Such meetings often take place over 1–2 days; therefore, depending on the length and location of the meeting, travel to and from the meeting may be completed in a single day, or an overnight stay may be necessary.

2 How will subjects be recruited? What is the screening process for subjects – are subjects easily found, or will they be identified by medical chart review?

3 How much time will be required to perform protocol-related activities? For example, if the protocol requires enrollment of 5 subjects per month and subjects must be seen every 2 weeks for approximately 15 minutes per visit, then 2.5 hours of investigator time per month must be set aside to meet with study subjects. An additional 3–4 hours per month should be allocated for performing other aspects of the study (e.g., meeting with the CRC to review study progress and answer questions; reading study updates; reviewing and signing required forms; and meeting with the study monitor during periodic site visits). In this example, a minimum of 6 hours per month of investigator time should be allocated to the study.

4 How much time will be required to train subinvestigators regarding the study and activities? Does the sponsor require study-specific training (e.g., to perform ophthalmologic examinations or complete psychological assessment tools)?

Clinical Research Coordinator and Other Study Personnel

A review of the protocol will help determine tasks that can be delegated to study personnel, as well as whether there will be requirements for time, skills, and/or personnel above those available from existing clinical research staff.

Clinical Research Coordinator

To evaluate the total amount of work hours needed for a trial, estimate the amount of time required to perform each of the protocol-related activities.

1 How many groups of personnel will need to be trained in study procedures by the CRC? Will subjects be seen in the acute care setting, requiring all shifts to be trained? Are subjects likely to be found on more than one unit in the hospital or clinic? Should laboratory personnel or other technicians be made aware of protocol requirements? Will pharmacy personnel need training?

2 Where in the hospital will you find prospective subjects with this disease process (e.g., is your subject a cardiology patient who may be found on 1 or 2 units in the hospital, or a hematology patient who could be on any medical or surgical unit)? Who will screen the prospective subject, and how long will that typically take?

3 In a clinic-based study, how much time will be needed to review medical records to screen potential subjects? Will the CRC need to talk to staff in other clinic departments to increase awareness of the study?

4 Will the CRC be responsible for preparing or administering study drug, or will hospital pharmacy staff prepare study drug for nursing staff to administer?

5 Will the subject require any additional procedures or interventions after receiving study drug, such as recording vital signs or drawing blood samples? Will the CRC or other staff members perform these activities?

6 Will there be outpatient or follow-up visits? If so, how many, and at what intervals? Will the CRC need to schedule visits and protocol-required tests? How much time will the typical visit require of the CRC?

7 How many pages are in the subject's case report form? Approximately how long will it take to complete? Will data be entered electronically? Is the CRC familiar with electronic data entry?

8 Are most of the data collected for the study routinely documented in the subject's medical chart, or will additional worksheets be used for data collection? Will data need to be obtained from transfer hospitals or referring physicians' offices?

9 Does the study use electronic data capture (EDC)? Do study personnel have access to a secure high-speed Internet connection for data entry? Will the CRC need to be trained in using EDC

tools? Will training be provided on-site, or will the CRC need to travel to the sponsor (or designee) for training?

10 What is the process for reporting serious adverse events (SAEs), and how much time per week will it likely require?

11 How frequently will on-site monitoring visits be conducted? How much time will be required of the CRC for each monitoring visit? One day or more? How much time will be needed to order medical records, prepare for the monitoring visit, and organize meetings with the monitor and PI?

Support Staff

Depending on the type of study, the amount of paperwork, and the scheduling of subjects and procedures involved, support staff are usually needed to perform administrative duties and assist the site study team.

1 Are there administrative duties, such as the scheduling of subjects or procedures, that can be managed by support staff?

2 If medical records need to be requested and/or photocopied, can this be done by support staff?

Pharmacist

Some institutional policies require a pharmacist to handle all investigational drugs. Some studies require the participation of a pharmacist; for example, to prepare intravenous study drug in order to maintain the study blind.

1 Will study drug need to be prepared by a pharmacist?

2 Does the protocol require that study drug be stored in and dispensed from the pharmacy?

3 If refrigeration is required, is locked, access-controlled refrigerated storage available for the study drug?

4 Will the pharmacist maintain the drug accountability records?

Laboratory Tests and Procedures

Laboratory samples can be a critical component of clinical trial data. Some studies require numerous blood, urine, and other types of samples. Use of central laboratories, which require that samples be shipped off-site for analysis, is common.

1 Will a local (within the institution) or central laboratory (off-site), or both, be used for specimen analysis? How many samples must be obtained, and at what intervals?

2 Are these protocol-required lab tests normally performed at the investigative site? Will lab personnel need to be trained to process and label specimens? Are there drug levels or other specialized tests requiring special handling and shipment to a central core lab?

3 Do lab personnel who will handle or process study samples have the required training and certification; for example, a Dangerous Goods Certificate?

4 Do the lab samples require special handling (e.g., –70°C freezer storage or cold centrifuge) that is not readily available? Will the sponsor provide any equipment your site lacks?

5 Will samples be handled and processed on weekends or during the night?

6 If specimens are stored at the investigative site and then shipped in batches, is adequate storage available?

7 Are there special shipping or handling requirements, such as packing specimens in dry ice or special containers? Are these provided by the sponsor or available within your institution?

8 Are there procedures that require the cooperation of other departments at the site? Do the personnel in the other departments need training?

9 Are you required to submit "test sample data" to ensure standardization across sites for specific equipment to be used in the study; for example, test data for a "dummy subject" in a nuclear imaging study?

10 Are there other central or "core" labs that require shipment of subject data? For example, is there an electrocardiogram (ECG) core lab to which all ECGs must be sent for interpretation, or an x-ray core lab to which all films must be sent?

Additional Space and Equipment

All clinical trials require space and equipment to be dedicated to the study. These include shelf or file cabinet space to store study files, subject binders, and other study materials; documents will require long-term storage at the time of study completion. Access to equipment including a telephone, computer with high-speed Internet access, facsimile (fax) machine, and photocopier is often an absolute requirement. However, a specific protocol may require storage, space, or specific modes of communication in addition to those already available. If available space and equipment at your site do

not meet the trial requirements, determine whether the additional resources can be obtained from the sponsor (or other sources).

1 Will study supplies (data forms and regulatory files) need to be stored for a longer-than-usual period and require more office and/or storage space? Is there secure space within the institution or at an off-site location for long-term storage of study documents?

2 Is remote data entry via computer required for the study? Will the sponsor supply the computer? Is there adequate workspace for the computer and is high-speed Internet access available?

3 Will study drug be stored in the pharmacy, the office of the CRC or PI, or elsewhere in the institution? If so, is there adequate locked storage space available for the study drug?

4 Do you need equipment such as centrifuges, refrigerators, or freezers not currently available at your site? Will the sponsor provide these?

Budget Considerations

It is important to determine the amount of reimbursement from the sponsor and how the payments will be made throughout the study. The reimbursement plan may affect your site's ability to participate in the study, although there are ways to minimize expenses, and high enrollment may help offset costs. Some questions that pertain to the study site agreement or Contractual Agreement with the study sponsor are:

1 If there are IRB submission fees, will the sponsor cover the cost?

2 Will the sponsor provide money to cover the cost of personnel time to prepare for study start-up and enrollment? Will the sponsor pay for time required to archive data and close out the study?

3 How often will site payments occur? What milestones (such as randomization, subject visits, completion of case report forms, completion of follow-up, and query-clean data) must a site reach to generate a payment?

4 Will the sponsor pay for subjects who are screened but determined to be ineligible for enrollment?

5 Are payments prorated when a subject withdraws from the study early?

6 Can the budget be amended if the site incurs additional costs due to protocol amendments? For example, extending the number of subjects to be enrolled and adding tests or procedures will add to the time/costs of a study.

7 In a device trial, who will pay the cost of the device? Will Medicare or private insurance cover the charges?

8 Is the time required to train the PI to use or insert a device reimbursed by the sponsor?

9 Does the device trial require extended follow-up and post-marketing surveillance?

10 If a device trial requires subjects to have additional invasive procedures to assess how the device is functioning, who will pay for the procedure?

Payment plans may be arranged in installments with defined timepoints for issuing payments. For example, 10% of the overall study payment might be made when all regulatory documents are submitted and the contract is signed, with an additional 60% to be paid when all subjects are enrolled at a site; the final 30% would be paid when all subjects have completed final visits and all subject data forms have been submitted and queried.

Other factors to consider when preparing a final study budget might include payment to the pharmacy for services provided or storage of study products; the cost of shipping samples to outside laboratories; and reimbursement of subjects' travel, overnight accommodations, and parking charges. Will you need to advertise for subject recruitment; if so, where and how (e.g., newspaper, posters, radio, television), and what will the costs be? Will there be charges for off-site storage of study materials after study completion? A thoughtful review of the protocol will identify most of the potential costs and charges.

Preparing a Budget

A clinical trial budget will help you determine if a specific protocol is economically feasible. The budget should be based upon a complete list of all activities performed for the protocol. It should include subject charges for protocol-required tests and procedures, study personnel costs, and institution charges, plus all other applicable costs. A final budget containing the site's actual costs can then be compared with the reimbursements that would be received from the sponsor or grant to determine whether undertaking the trial is financially feasible.

Review the **Schedule of Assessments** included in the protocol to obtain a summary of examinations, lab tests, and procedures that are required throughout the study.

- Carefully estimate the time commitment for the CRC, PI, and other study personnel.
- Include institutional overhead.
- Include payment for subjects who are found ineligible upon screening.
- Include funds for advertising and recruiting subjects.
- Include a provision for additional fees or costs related to protocol changes that increase time and workload.

Can You Negotiate Lower Fees to Reduce the Cost at Your Site?

After the costs of required tests and procedures have been obtained, identify areas where fees can be negotiated.

- Is the laboratory willing to process samples at a reduced "research" rate?
- Are your colleagues willing to waive or reduce professional fees for research-related consultations?
- Does the pharmacy have a reduced fee for research-related activities?

Once the costs for each test and procedure have been finalized, multiply the cost of each item by the number of times it will be performed. This provides the total cost of a subject's participation in the study.

Subject/Patient Charges

Review the protocol to identify all tests and procedures required for participating subjects. The *Schedule of Assessments* provided with the protocol is a good tool for identifying these procedures. Be sure to separate procedures and/or tests considered standard treatment that will be performed in the target population regardless of participation in the study; the costs of such procedures should not be included in the study budget since they should be covered by the subject's insurance carrier. Once the protocol-required procedures and tests have been identified, the next step is to determine the costs associated with each task. A good resource to determine actual costs is the institution's billing or accounting department.

Personnel Costs

In order to develop an accurate budget, a careful review of the protocol will reveal procedures and tasks required of the investigator and study personnel throughout the trial, from study start-up through close-out. When evaluating personnel time, it is important to consider the number of subjects to be enrolled and how long it will take to achieve the target enrollment. Be certain to evaluate carefully all aspects of a trial that will affect personnel time requirements. For example, an inpatient trial may require more CRC time than an outpatient trial because of the time needed for daily rounding on enrolled subjects and discussions with the hospital staff and attending physicians. Another trial may require fewer CRC hours to record data because the case report form is shorter.

Institution Charges and Indirect Costs

Institutions acting as an investigative site for a clinical trial often charge an "overhead" (or indirect costs), typically a percentage of the total expenses associated with the study. Indirect costs may include: utilities such as electricity, telephone, and Internet access; maintenance and cleaning; and equipment and administrative support. Other institutional charges may include a pharmacy department charge for pharmacist participation or study drug storage. Overhead charges are often 15%–25% or more of the total budget; you should check with your institution to determine the appropriate figure for your budget.

The final study budget should also reflect expenses such as anticipated telephone calls, subject travel expenses, paper supplies, and other miscellaneous items. Examples are included in the following section on how to prepare a budget.

Figure 10.1 Sample Subject Budget

Procedures	# Units Required	Unit Cost	Total Cost
ECG	3	_____	_____
CBC	2	_____	_____
Chest x-ray	1	_____	_____
Pharmacy dispensing	4	_____	_____
Parking passes	4	_____	_____
Total Cost Per Subject		_____	_____

Budget Planning

Subject Charges

List procedures and tests that are outside or in addition to those required for standard care as well as other per subject expenses.

Personnel Time

The chart on the following page is an example of how to determine personnel time based on a projected enrollment of 2 subjects/week. In this example, the CRC would spend approximately 20 hours/week once the start-up phase was complete. Time spent with the monitor during on-site visits would be in addition to the 20 hours/week during the enrollment and maintenance phases of the study. The investigator would spend approximately 2–4 hours/week for study-related activities and support personnel would spend 1 hour/week.

To accurately calculate the cost of personnel time, you need to know the duration of the study. Is it based on enrollment across all sites, or will you stop enrolling once you have enrolled an agreed-upon number of subjects at your site? You must also know the length of the follow-up period. For example, you plan to enroll 20 subjects over 10 weeks, each subject's active phase lasts 10 weeks, and there is a 10-week follow-up period for each subject. Allowing 6–8 weeks for data cleanup and study closeout brings the duration to a minimum of 36 weeks. Before enrollment, there may easily be 8–12 weeks (or more) required to sign the study contract, prepare and submit IRB documents, obtain IRB approval, attend a start-up meeting, train study personnel, and complete other preparatory activities.

Figure 10.2 Sample Personnel Budget

Personnel	Activity	Estimated Time	Study Phase	Unit Cost	Total Hours	Total Cost
CRC	Review protocol; prepare and submit documents to IRB	8 hours	Start-up		8 hours	
	Prepare and perform staff education	3 hourspreparation; 1 hour x 3 presentations	Start-up		6 hours	
	Prepare study-specific materials	6 hours	Start-up		6 hours	
	Screenand enroll subjects	1 ½ hours/subject	Enrollment and maintenance		3 hours/wk	
	Conduct follow-up visits	1 hour/subject	Enrollment and maintenance		6 bi-weekly visits x number of subjects	
	Process and ship laboratory samples	1 hour/subject/week	All phases		2 hours	
	Complete CRF and other data collection forms	6 hours/subject	Enrollment and maintenance		6 hours x number of subjects	
	Resolve data queries	2 hours/subject	Maintenance and close-out		2 hours x number of subjects	
	Communicate with sponsor	1 hour/week	All phases		1 hour per week throughout trial	
	Prepare for and participate in monitoring visits	2 hours/subject	All phases		2 hours x number of subjects	
	Archivestudy documents	8 hours	Close-out		8 hours	
PI	Review protocol	2 hours	Start-up		2 hours	
	Present protocol at IRB meeting	1 hour	Start-up		1 hour	
	Meet with colleagues	2 hours	Start-up		2 hours	
	Perform Initial Screening Visit for enrolledsubjects	1 hour/subject	Enrollment and maintenance		1 hour x number of subjects	
	Performfollow-up visit	20 minutes/subject visit	Enrollment and maintenance		6 bi-weekly visits x number of subjects	
	Communicate with sponsor and staff	1 hour/week	All phases		1 hour per week throughout trial	
Pharmacist	Prepare study drug; maintain accountability	1 hour/week	Enrollment		1 hour per week during enrollment	
Support Staff	Contactenrolled subjects as a reminder of visits	½ hour/week	Enrollment and maintenance		½ hour/week	
	Fax documents; request medical records	½ hour/week	All phases		½ hour/week	

Supplies

Determine whether laboratory samples need to be processed, shipped, or stored on-site. Processing specimens may not only be an expense in terms of personnel time, but may also require purchase and set-up. A centrifuge, special reagents, and specific supplies to obtain samples may be necessary. Samples may require shipping on dry ice or may need to be shipped internationally using a courier. On-site storage may entail special facilities or freezers. Whether the cost of these must be borne by the investigative site or whether they will be provided by the study sponsor must be determined and included in your budget.

Equipment

In addition to site supplies, you must determine if you have all the equipment necessary for the study. You may need to evaluate office equipment such as computers, high-speed Internet access, fax machines, storage cabinets for data forms, and determine whether additional equipment needs to be purchased.

Negotiating a Budget

Besides the protocol-required procedures, there are many variables in the contract that will affect your decision to conduct the study at your site. You will need to determine if there will be non-reimbursed IRB fees or costs for advertising. You should ask whether the sponsor will pay for screening tests performed in prospective subjects who are determined to be ineligible. Will the sponsor pro-rate payments for subjects who withdraw early or who are lost to follow-up? Identify the milestones that will trigger payments and decide if adequate funds will be available between payments.

If you are allowed some flexibility in negotiating your contract with the sponsor, you might consider asking for an up-front payment (for example, 10% of the budget) to defray the costs of study start-up, including preparing and submitting regulatory documents, developing your screening and recruitment strategy, attending off-site investigator meetings, and participating in an on-site initiation visit. You might also consider asking for payments based on milestones such as procedures performed or data submitted, rather than one lump-sum payment at the completion of a subject's participation. Another option is to ask for monthly payments throughout the study to ensure that your site receives funds at regular intervals.

Should We Do this Study at Our Site?

Finally, after reviewing the protocol and determining its feasibility at your site, ask yourself: "Do I really want to participate in this trial?" The answer to this question may be one of the most important factors in determining the success of a trial. Consider whether this study will be of interest throughout its duration – it will be difficult to maintain enthusiasm if the product being studied or the question to be answered is of no clinical interest to you. Lack of interest by the PI or co-PI, colleagues, and study personnel can result in poor subject enrollment and reduced trial revenue. It can also affect future opportunities to participate in clinical trials if sponsors view this work as representative of your site. If you and your colleagues are excited and highly motivated to conduct the study, your study performance will be enhanced accordingly. Enthusiastic participation will help ensure a successful study and continued sponsor interest in you and your site.

11 Study Activities

In this Chapter

- Step-by-step instructions to guide you through a trial from start-up to close-out
- Useful tips for every phase of the trial
- Sample documents to help the trial run smoothly at your site

"Never mistake motion for action."

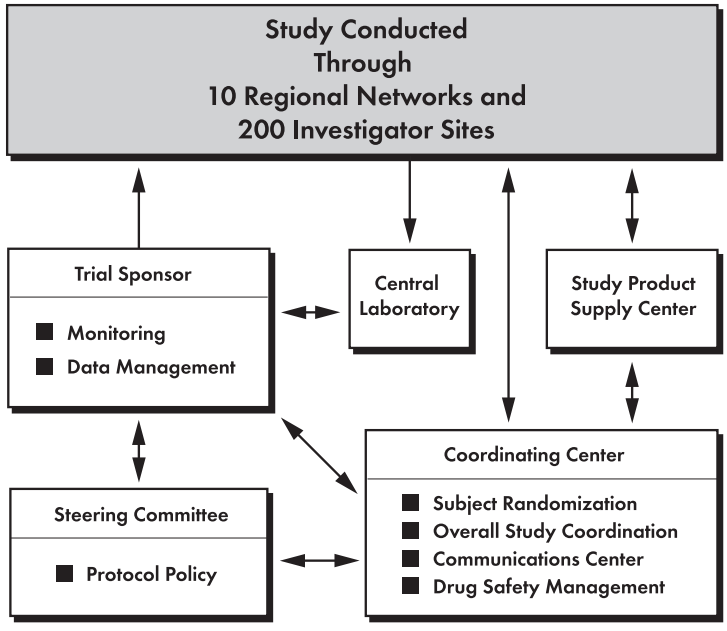
Ernest Hemingway (1899–1961), Nobel Prize-winning author

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

Each trial has its own infrastructure of individuals and groups who are responsible for different aspects of the study. Sponsors may assign roles and delegate responsibilities within a clinical trial in numerous ways. These organizational decisions are usually made during the protocol development phase of the trial. Responsibility for aspects such as site monitoring, safety reporting, investigational product distribution, site management, and data management may be divided among several groups, including Academic Research Organizations (AROs), Contract Research Organizations (CROs), Site Management Organizations (SMOs), and the sponsoring organization.

The organizational structure will vary from one trial to another based on protocol needs, financial considerations, and logistical issues. While there is no single best way to organize roles and responsibilities within a clinical trial, it is important to be aware of the different groups involved and understand the roles and responsibilities of each. Regardless of the overall organizational structure of the trial, your site's success will depend on a plan that takes into account the uniqueness of your site and study personnel, and how best to integrate your site into the overall study structure.

Figure 11.1 Sample Organizational Chart



Study Start-up Phase

The start-up phase of a study encompasses the time from when the Principal Investigator (PI) agrees to participate until the first few study subjects are enrolled. During this phase many activities must occur before the first subject can be enrolled. There is no set order for performing these activities; you will most often work on many of them simultaneously. During start-up, the PI, Clinical Research Coordinator (CRC), and other study personnel should collaborate to draw upon their ideas and previous experience to develop an effective plan for conducting the study. Planning done during this phase will pay off later in areas such as subject recruitment and data collection. The following activities are typically performed during the start-up phase.

Review the Protocol, Develop a Budget, Prepare Documents for IRB Submission

After being approached to participate in a clinical trial, you will review the protocol and develop a budget to determine the feasibility of conducting the study at your site. The CRC typically assists the PI in these activities. Once you agree to participate in the clinical trial, you will need to submit the required regulatory documents to the sponsor or their designee.

Sponsor documents typically include:

- Signed confidentiality agreement
- Signed protocol and applicable amendments
- Indemnification agreement
- Financial contract
- Completed and signed Form FDA 1572 or Investigator Agreement
- Financial disclosure forms for the PI and others listed on the Form FDA 1572 or Investigator Agreement
- A *curriculum vitae* (CV) for any person listed on Form FDA 1572 or Investigator Agreement
- Current clinical laboratory certification and normal values

If you need to hire a CRC, you should do so quickly in order to aid study planning and preparation. A primary activity early in start-up is the preparation of documents for submission to the Institutional Review Board (IRB); the PI often delegates this activity to

the experienced CRC. If the sponsor has provided a template for a consent form, you should personalize the form with details applicable to your site, including the name of your institution, the PI's name, and appropriate contact information.

Documents for submission to the IRB include:

- Protocol (and amendments if any)
- Investigator's Brochure or package insert for a marketed drug or device
- Consent form; assent form if minors will be subjects (consent form/assent form should be dated, paginated, and labeled in the footer)
- Recruitment materials, including copies of proposed recruitment notices or flyers; scripts for radio or television advertisements; informational pamphlets
- Subject educational materials
- Surveys and questionnaires that will be administered to subjects
- Payment or compensation plan for subjects

IRBs often provide a submission checklist or require a cover letter to accompany all documents being submitted. Check with your IRB to obtain a complete list of required documents.

Once IRB approval is obtained for the study, the sponsor must be sent a copy of the letter documenting IRB approval of the protocol and applicable amendments, consent documents, advertisements, subject educational materials, and any other relevant documents.

Establish the Site Study Team

One of your first responsibilities as an investigator is to establish a site study team, which should include representatives from departments with protocol-related responsibilities. In addition to the CRC, you will need to determine what other personnel are necessary to effectively conduct the study. With the assistance of the CRC, you should carefully review the protocol and consider the organization of your institution to answer questions such as:

Where will subjects be identified?
When potential subjects will be identified in an outpatient clinic or on specific inpatient units, it may be helpful to include personnel from those areas on the study team. Their knowledge and understanding of issues related to their specific areas may help you develop a better screening and recruitment plan.

Do laboratory samples need to be handled or processed differently from the laboratory routine?
When special handling or techniques are required, a laboratory supervisor or designated laboratory technician may be identified as a contact person, or included on the study team.

Do procedures required for the study need to be performed or documented in a particular manner?
Trial-related procedures may require non-routine tasks or documentation on specific forms. Personnel from areas where study procedures will be performed may be able to contribute suggestions to ensure that protocol-designated procedures are followed. For example, if the protocol requires a bicycle exercise test to be performed at a specific pedaling speed or for a pre-specified time period, the technician who routinely sets up the bicycle tests may have some suggestions on how to ensure that the test is always performed according to protocol.

Can a pharmacist assist with study drug-related issues, drug storage, and drug dispensing?
The pharmacist may have previous clinical trial experience and be able to provide assistance with study drug issues.

Does the study device need to be stored in a special location?
A device that requires surgical implantation may need to be stored in a surgical suite; therefore, a designated member of the surgical staff may need to be involved in the planning.

Is there a behavioral intervention that requires staff to have special skills, licensures, or training?
The study intervention may require a counselor or technician with special training or licensure. For example, a protocol examining Cognitive Behavioral Therapy (CBT) may require that study counselors be certified to perform CBT. Or a protocol may simply require the study counselor to have a certain number of years of professional experience working with a given population (e.g., substance abusers or adolescents).

After you have identified the study team and delegated study activities to the appropriate personnel, it is important to document this on a *Signature and Delegation Log*. This log should indicate who will be carrying out study activities such as screening subjects, obtaining informed consent, recording data, and dispensing supplies, among others.

Once you assemble the site study team, methods of communication should be determined, as regular communication throughout the study will be integral to success. During the start-up phase, frequent

Figure 11.2 Sample Signature and Delegation Log

HEAT
Hypothetical Example of A Trial

HEAT Signature and Delegation Log

Sponsor: HEAT	Sponsor protocol number: 2468-00
Test product: Clotbuster or Placebo	
Investigator name: Address:	Site number: __ __ __

Name of Site Personnel	Role	Signature	Initials	Start Date	End Date	Tasks (indicate using codes below)	PI Authorization (Initials)
	PI						

A. Informed consent
B. Physical examination-**MD only***
C. Inclusion/exclusion criteria assessment
D. Randomize subjects
E. Test product dispensing and accountability
F. eCase Report Form (eCRF) completion and correction
G. Sign-off data queries

H. Vital signs
I. Adverse event interpretation-**MD only***
J. Specimen collection (blood, ECG, etc.)
K. Exam result interpretation (labs etc.) **MD only***
L. SAE reporting
M. Other:_____

Roles
PI: Principal Investigator
SI/Co-I: Sub-Investigator/Co-Investigator
CRC: Clinical Research Coordinator
PH: Pharmacist
Other: _____

* Or licensed practitioner

	Principal Investigator	Signature of Principal Investigator	Date
At end of study, PI must confirm all above information is correct and sign.			__ __ /__ __ __ /__ __ __ __ dd mmm yyyy

(usually weekly) face-to-face meetings may be necessary while developing the study plan. Eventually, meeting frequency may decrease as the trial progresses. Sharing study newsletters, enrollment updates, and other communications related to the trial is a good way to keep the study team enthusiastic and informed. Study meetings during the start-up phase might include discussions about enrollment, recruitment issues and strategies, logistical issues such as study-required procedures, and communication from the sponsor. Record and distribute meeting minutes to all team members and keep a copy of the minutes in your study file.

Participate in Investigator Meetings

Many sponsors conduct Investigator Meetings before or just after the first subjects are entered into the study. These meetings sometimes serve as a general "Initiation Visit" (see Chapter 7) with the purpose of educating PIs and CRCs in the details of the study. One advantage of reviewing the protocol and required procedures at an Investigator Meeting is that questions and discussions raised by individual PIs and CRCs can benefit the entire group.

Usually, each site's PI and CRC are invited to attend the Investigator Meeting, which lasts 1–2 days. Some sponsors also invite other site personnel, such as the site pharmacists, who may have an integral role in the study.

Investigator Meetings usually begin with an overview of the study, followed by background information pertinent to the protocol and study treatment. They then progress to a discussion of specific protocol details, including data forms, reporting of serious adverse events (SAEs), and issues unique to the trial. While some sessions are geared toward the CRC, who often performs many of the trial-related activities, the PI will also benefit from sessions that reveal the logistical demands of the protocol, review SAE reporting requirements, and provide opportunity for clinical discussions.

Many investigator meetings are conducted regionally, affording the opportunity to meet PIs and CRCs from other participating sites located within the same geographic area. These contacts may provide opportunities for additional sources of ideas or information when trying to resolve protocol-related issues in the future, and may also be an asset when study subjects are transferred between institutions.

Develop a Recruitment and Enrollment Plan

Establishing an effective plan for identifying, screening, and enrolling subjects will depend greatly upon the subject population, the type

of trial, and the individual site. Some items that are part of your recruitment and enrollment plan will need IRB and sponsor approval before use. This includes materials and information that will be viewed and used by subjects, such as advertisements and informational pamphlets.

Develop a Plan to Identify Potential Subjects

You may be able to identify subjects within your own medical practice or institution; however, your recruitment plan may need to include health care professionals outside your institution as well as members of the community at large. It will be important to provide information about the study to colleagues who may have contact with the target subject population and are therefore well-placed to identify potential subjects. You may consider sending a letter to colleagues that provides a study summary, noting the sponsor, start date, subject procedures, and how to contact you with information regarding potential subjects. Assure colleagues and referring physicians that subjects will continue to be seen by the referring physician for continuing care outside of the study. After enrollment, send relevant updates regarding the subject's study participation to referring physicians and keep the channel of communication open with colleagues.

You may also wish to consider public advertising to recruit subjects into the study. To create a general awareness and understanding of the trial, you may choose to create radio, television, electronic, or newspaper advertisements. Announcements can be sent and presentations can be made at local businesses, worksites, and community groups. Public education can heighten awareness of the disease prevalence, the investigational product, and potential outcomes. Flyers can be posted at local grocery stores, pharmacies, or medical supply stores. Advertisements should be simple and limited to information a subject needs to know to determine eligibility and interest, and must be reviewed and approved by the IRB before use.

Develop Advertising Tools

The FDA views recruitment of subjects as an extension of the informed consent process and requires advertisements to include the following elements:

1 Name and address of the PI and research facility conducting the study;

2 Purpose of research and summary of the eligibility criteria for study enrollment;

3 Condensed description of the benefits enrolled subjects receive;

Figure 11.3 Sample Advertisement

Do you take insulin for your Diabetes?

Have you taken insulin for more than 1 year?

Do you take a single dose of insulin in the morning?

Do you test your blood sugar daily?

If you are between 40 and 80 years of age and meet study criteria, you may be eligible to participate in a research study of an investigational medication at your local hospital. A new type of insulin is being evaluated for the treatment of insulin-dependent diabetes. Study medication and physical assessments will be provided free of charge for this 90-day study. For more information call <*local contact name*> at <*phone number and hospital name*>.

4 Time commitment required of subjects;

5 Contact name and number for additional information.

According to the regulations, advertisements should not:

- claim that the test product is safe or effective for the indication under investigation;
- use the terms "new treatment," "new medication," or "new drugs" without explaining that the test article is investigational [21 CFR 312.7a];
- emphasize financial rewards for study participation, such as money paid to the subject or free medical treatment, which may be viewed as coercive to financially-constrained subjects.

Rules for advertisements apply to all advertising media, including radio, television, and information posted on the Internet. The same is true for educational materials that will be viewed by subjects, including educational pamphlets and information sheets listing study activities and subject responsibilities.

Develop a Plan to Screen Potential Subjects

Depending on the type of study, you may be able to screen potential subjects before enrollment to determine if they are eligible for study participation. You can review the potential subject's medical records to ensure that preliminary entry criteria are met before approaching the subject. For example, if an eligibility criterion is a fasting serum

Figure 11.4 Screening Log

HEAT
Hypothetical Example of A Trial

Screening Log

Site #: __ __ __ Page __ of __

Record information for all subjects screened

Date of Screening	Screening Number	Initials	Sex	Age	Enrolled?	Comments or Reason(s) Not Enrolled (Use codes listed below)
__ __/__ __ __/__ __ __ __ dd mmm yyyy	__ __-__ __	__ __ __	❑ M ❑ F	❑ ≤ 75 ❑ > 75	❑ Yes ❑ No →	
__ __/__ __ __/__ __ __ __ dd mmm yyyy	__ __-__ __	__ __ __	❑ M ❑ F	❑ ≤ 75 ❑ > 75	❑ Yes ❑ No →	
__ __/__ __ __/__ __ __ __ dd mmm yyyy	__ __-__ __	__ __ __	❑ M ❑ F	❑ ≤ 75 ❑ > 75	❑ Yes ❑ No →	
__ __/__ __ __/__ __ __ __ dd mmm yyyy	__ __-__ __	__ __ __	❑ M ❑ F	❑ ≤ 75 ❑ > 75	❑ Yes ❑ No →	
__ __/__ __ __/__ __ __ __ dd mmm yyyy	__ __-__ __	__ __ __	❑ M ❑ F	❑ ≤ 75 ❑ > 75	❑ Yes ❑ No →	

Use the following codes to indicate the reason(s) the subject was not enrolled.

Exclusion codes:

1. Meets all inclusion/exclusion criteria but does not wish to participate
2. Is less than 18 years old
3. Has no ischemic symptoms
4. Onset of symptoms greater than 6 hours prior to enrollment
5. Is not expected to undergo PCI
6. ECG was not indicative of acute STEMI
7. Subject not able to provide informed consent
8. Unable to be followed for 3 months for evaluation
9. Evidence of active infection

glucose >120 mg/dL, and the result of a fasting serum glucose is in the medical record, you can determine if this criterion has been met. However, if additional tests are required to determine study eligibility, you must obtain signed informed consent from the subject before performing any of these additional tests. Sometimes a subject will meet preliminary criteria for enrollment, but further testing reveals an exclusion criterion. The subject should have signed a study consent form which includes permission to perform the screening tests, which in some cases will ultimately result in the subject's exclusion from the study. This is often referred to as a "screening failure."

In some studies it is not possible to screen subjects before enrollment. For example, in some behavioral studies, subjects often give informed consent for enrollment before screening questionnaires to determine eligibility can be administered.

To document subjects screened for study inclusion, you may be asked to complete a Screening Log that identifies all potential subjects screened and indicates: 1) subjects screened but determined to be ineligible; 2) eligible subjects approached for study participation who declined to participate (and for what reasons); 3) and eligible subjects who chose to participate. In this way, the Screening Log can be used as a tool to show that research subjects were enrolled without bias, which is particularly important when women and minorities are required to be included. To meet regulatory requirements for privacy of protected health information, the Screening Log should be de-identified; for example, by using the subject's initials and a designated study number or screening number.

Identify Potential Barriers to Recruitment

Based on the study population, try to identify barriers to subject recruitment and enrollment. For example, in a study that includes women between the ages of 20 and 50, you may need to help potential subjects solve logistical barriers related to child care, transportation, meals, and timing of study appointments. In a study involving exercise in elderly heart failure patients, you may encounter subjects who need help with transportation to study visits, support of sick spouses, or who believe that exercise is "only for younger people." Possible solutions may include discussions regarding family support for child or elder care, locating a van pool or volunteers to provide transportation, and the use of a recumbent exercise bicycle instead of a treadmill or upright bicycle. Subjects with language barriers or who are illiterate will need help from someone who can speak fluently in their native language and provide translation support throughout the study period.

Develop a Plan to Enroll Subjects

Once you have identified and screened subjects, obtained informed consent, and confirmed that all eligibility criteria are met, you will need to enroll the subject.

When developing the enrollment plan, consider creating an "Enrollment Packet" for use when subjects are identified. Place the packets in the locations where subjects will be screened and enrolled. To determine which forms should be included in the packet, review the steps of the screening and enrollment process for the study.

Documents and forms to consider placing in the enrollment packet include:

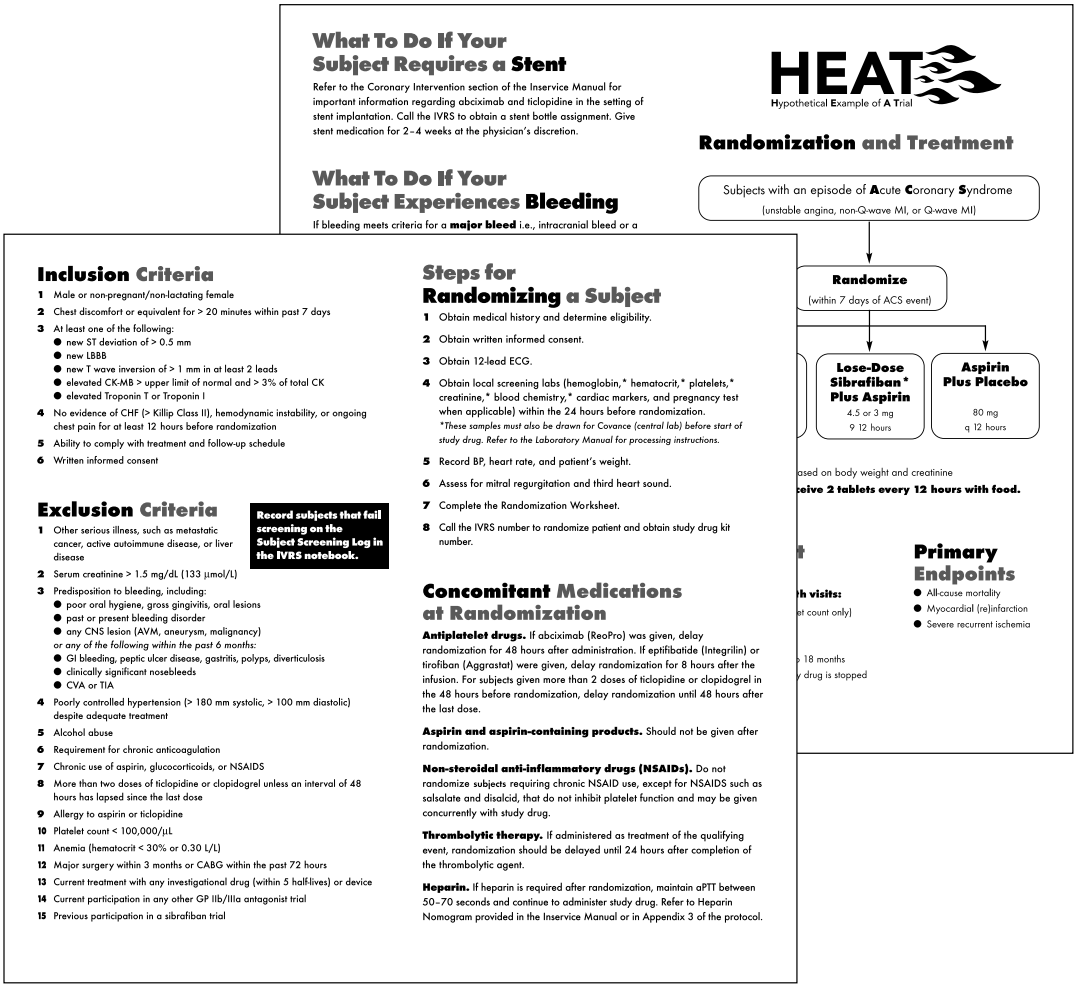
- Screening/enrollment forms
- Consent form
- Authorization for release of medical records and use of protected health information
- Subject contact information sheets
- Worksheets created for study-related procedures
- Physician orders for study-related procedures and tests

In acute trials where enrollment must occur within a narrow time frame, a number of tools have proven helpful in quickly screening and identifying subjects. One of these is a pocket reference card for physicians and nurses that outlines eligibility criteria and provides a quick review of protocol-required procedures. Pocket reference cards can be distributed to all health care professionals who come into contact with potential subjects. Posters that provide the same information may be placed in a visible location in areas where staff work; strategic locations might include the doctors' office in a clinic, a staff lounge, or a dictation room. When randomization is performed by calling a specified telephone number, stickers with the randomization telephone number may be attached to the telephones at various locations.

Address Competing Trials at Your Site

One challenge to study recruitment is other trials at your site competing for the same subject population. When this occurs, enrolling sufficient subjects in your trial may be difficult. There is also a chance that selection bias can be introduced into one or both studies, since competing trials may promote an unconscious (or conscious) decision about which protocol better suits an individual subject. Therefore, if competing trials do exist at your site, try to make sure that enrollment in both trials is based on objective criteria.

Figure 11.5 Sample Pocket Reference Card



What To Do If Your Subject Requires a Stent

Refer to the Coronary Intervention section of the Inservice Manual for important information regarding abciximab and ticlopidine in the setting of stent implantation. Call the IVRS to obtain a stent bottle assignment. Give stent medication for 2–4 weeks at the physician's discretion.

What To Do If Your Subject Experiences Bleeding

If bleeding meets criteria for a **major bleed** i.e., intracranial bleed or a

HEAT
Hypothetical Example of A Trial

Randomization and Treatment

Subjects with an episode of **A**cute **C**oronary **S**yndrome
(unstable angina, non-Q-wave MI, or Q-wave MI)

Randomize
(within 7 days of ACS event)

Lose-Dose Sibrafiban * Plus Aspirin	**Aspirin Plus Placebo**
4.5 or 3 mg 9 12 hours	80 mg q 12 hours

ased on body weight and creatinine
eive 2 tablets every 12 hours with food.

h visits:
t count only)

18 months
drug is stopped

Primary Endpoints
- All-cause mortality
- Myocardial (re)infarction
- Severe recurrent ischemia

Inclusion Criteria

1. Male or non-pregnant/non-lactating female
2. Chest discomfort or equivalent for > 20 minutes within past 7 days
3. At least one of the following:
   - new ST deviation of > 0.5 mm
   - new LBBB
   - new T wave inversion of > 1 mm in at least 2 leads
   - elevated CK-MB > upper limit of normal and > 3% of total CK
   - elevated Troponin T or Troponin I
4. No evidence of CHF (> Killip Class II), hemodynamic instability, or ongoing chest pain for at least 12 hours before randomization
5. Ability to comply with treatment and follow-up schedule
6. Written informed consent

Exclusion Criteria

Record subjects that fail screening on the Subject Screening Log in the IVRS notebook.

1. Other serious illness, such as metastatic cancer, active autoimmune disease, or liver disease
2. Serum creatinine > 1.5 mg/dL (133 µmol/L)
3. Predisposition to bleeding, including:
   - poor oral hygiene, gross gingivitis, oral lesions
   - past or present bleeding disorder
   - any CNS lesion (AVM, aneurysm, malignancy)

   or any of the following within the past 6 months:
   - GI bleeding, peptic ulcer disease, gastritis, polyps, diverticulosis
   - clinically significant nosebleeds
   - CVA or TIA
4. Poorly controlled hypertension (> 180 mm systolic, > 100 mm diastolic) despite adequate treatment
5. Alcohol abuse
6. Requirement for chronic anticoagulation
7. Chronic use of aspirin, glucocorticoids, or NSAIDS
8. More than two doses of ticlopidine or clopidogrel unless an interval of 48 hours has lapsed since the last dose
9. Allergy to aspirin or ticlopidine
10. Platelet count < 100,000/µL
11. Anemia (hematocrit < 30% or 0.30 L/L)
12. Major surgery within 3 months or CABG within the past 72 hours
13. Current treatment with any investigational drug (within 5 half-lives) or device
14. Current participation in any other GP IIb/IIIa antagonist trial
15. Previous participation in a sibrafiban trial

Steps for Randomizing a Subject

1. Obtain medical history and determine eligibility.
2. Obtain written informed consent.
3. Obtain 12-lead ECG.
4. Obtain local screening labs (hemoglobin,* hematocrit,* platelets,* creatinine,* blood chemistry,* cardiac markers, and pregnancy test when applicable) within the 24 hours before randomization.
   **These samples must also be drawn for Covance (central lab) before start of study drug. Refer to the Laboratory Manual for processing instructions.*
5. Record BP, heart rate, and patient's weight.
6. Assess for mitral regurgitation and third heart sound.
7. Complete the Randomization Worksheet.
8. Call the IVRS number to randomize patient and obtain study drug kit number.

Concomitant Medications at Randomization

Antiplatelet drugs. If abciximab (ReoPro) was given, delay randomization for 48 hours after administration. If eptifibatide (Integrilin) or tirofiban (Aggrastat) were given, delay randomization for 8 hours after the infusion. For subjects given more than 2 doses of ticlopidine or clopidogrel in the 48 hours before randomization, delay randomization until 48 hours after the last dose.

Aspirin and aspirin-containing products. Should not be given after randomization.

Non-steroidal anti-inflammatory drugs (NSAIDs). Do not randomize subjects requiring chronic NSAID use, except for NSAIDS such as salsalate and disalcid, that do not inhibit platelet function and may be given concurrently with study drug.

Thrombolytic therapy. If administered as treatment of the qualifying event, randomization should be delayed until 24 hours after completion of the thrombolytic agent.

Heparin. If heparin is required after randomization, maintain aPTT between 50–70 seconds and continue to administer study drug. Refer to Heparin Nomogram provided in the Inservice Manual or in Appendix 3 of the protocol.

Two such methods are:

1 limiting enrollment in one trial to even days and the second trial to odd days; and
2 alternating enrollment in trials as eligible subjects are identified.

If entry criteria for the competing trials are slightly different, create a triage plan that helps you make a rapid decision regarding for which trial the subject is best qualified. These options are not perfect, and obviously reduce potential enrollment in both trials, but may be necessary if your site is involved in competing trials.

Develop Plan to Obtain Informed Consent

Beyond developing a plan focused on when and where subjects will be recruited and enrolled in a trial, it is important to consider factors

and activities that will generate interest in clinical trial participation and allow subjects to engage in discussions of trials in a comfortable setting.

Consider the following points when developing the plan for subject enrollment:

Conduct discussions about the trial in a private setting. Potential subjects might feel uncomfortable if others can overhear discussion regarding their health issues or diagnoses. When a private room is not available, move to a quiet corner of the clinic or some other space to provide privacy.

Review the trial activities and subject responsibilities slowly and carefully. As you review the consent form and other study materials, be sure to give the subject and family members time to ask questions. Explain procedures in terminology that the subject can understand so that the subject is not confused about what participation involves. Do not pressure the subject for a quick response, but instead give adequate time for decision making and allow time for potential subjects to discuss study participation with family members.

Have the PI, CRC, and other study personnel who will interact with the subject during the study meet the potential subject. In particular, effective interactions with the PI and CRC at this early stage will contribute significantly toward making subjects feel comfortable in deciding to participate.

Determine if additional study materials are needed to provide clear information to potential subjects. If a study is particularly complex or you are working with subjects who may have a limited educational background, consider whether the development of other informational items would be helpful in describing some of the study activities and subject responsibilities. Such materials, however, will require IRB approval before use.

Not all people approached for participation in a clinical trial will agree to participate. But if you have developed an effective plan for how and where information is communicated to potential subjects, subjects will be more likely to agree to participate, based on a good understanding of the study, the activities that will be required of them during the study, possible benefits and risks of harm, and all other relevant study aspects.

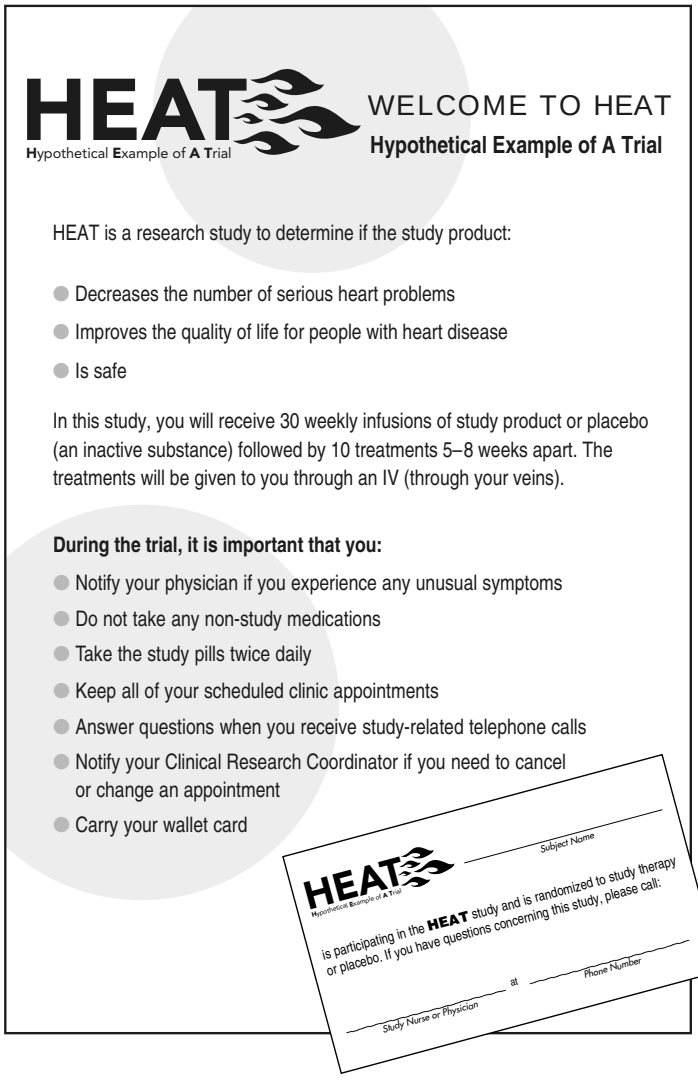
Develop Educational Materials for Subjects

You may find it helpful to develop or create a number of items that will provide study subjects with useful information regarding trial activities and the subject's responsibilities. The sponsor may provide

some of these materials, but you may also want to develop your own or adapt materials to meet the needs of subjects at your site. You will also need to check with your IRB to determine which items require IRB approval.

Wallet Card – this card indicates that the subject is participating in a clinical trial, listing the name of the study, the name and contact number of the PI, and who to call in case of an emergency. You may include other useful information on the card, such as symptoms to be reported immediately and medications or treatments to avoid.

Figure 11.6 Sample Subject Brochure and Wallet Card



Subject Brochure – this may include a brief synopsis of the study, listing follow-up visits and requirements. The brochure may include reminders of when and how to take medication, precautions while in the study, and who to call with questions or concerns. The study name, PI and CRC names and contact details, and hospital or clinic address should be provided.

Dear Health Care Provider Letter – a letter that explains the study in greater detail than the information included in the Wallet Card can be provided for subjects to give to other health care providers who subjects will visit for any type of medical or dental care during the course of the study. This is particularly useful in long-term follow-up studies.

Other Helpful Tools

- Pill container for study medication
- Calendar to track follow-up visits
- Magnet with study name/PI or CRC name/contact numbers – subject can use the magnet to keep an appointment card or other information in a convenient location
- Tote bag to carry study medications, diaries, study calendar, or other study materials when coming to each follow-up visit

Conduct Education and Training Sessions for Site Personnel

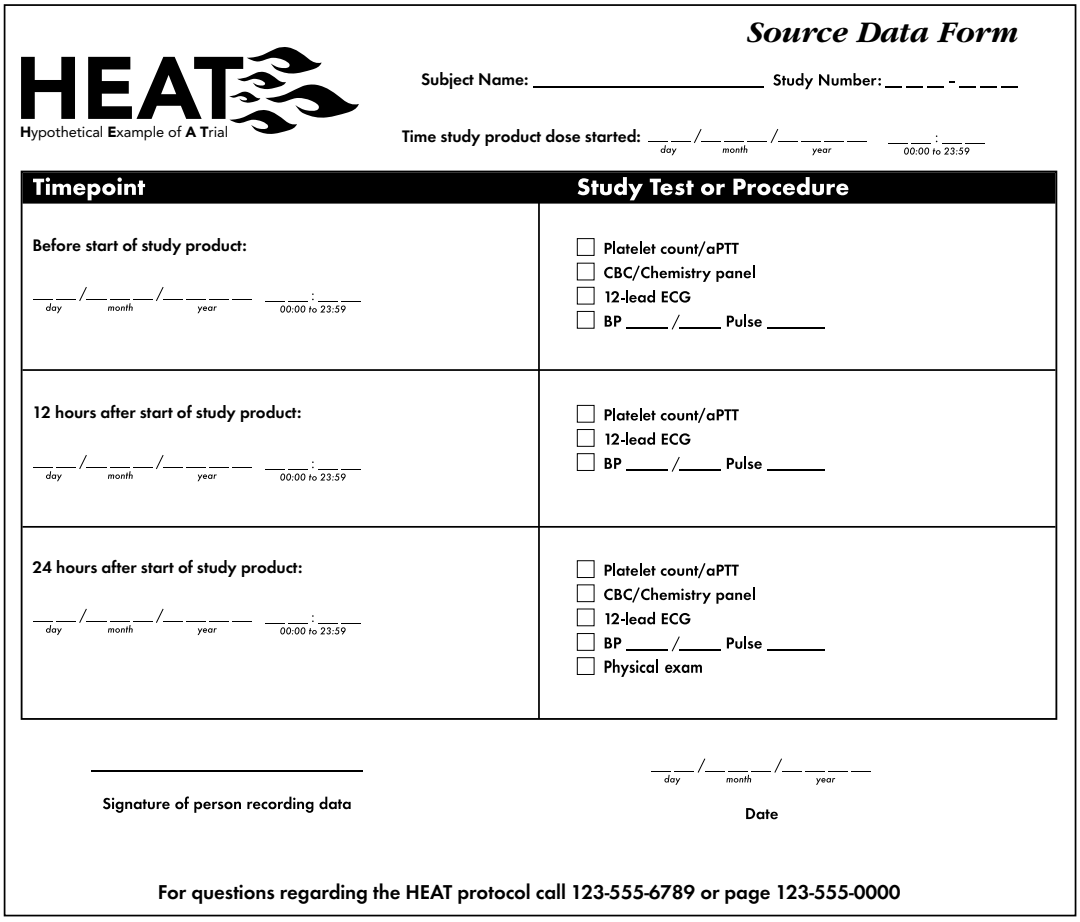
Once the enrollment plan has been established, it will be easier to identify site personnel who need to be aware of study procedures and details. If your study involves acutely ill or hospitalized patients, patient care staff on all shifts will need to be informed about the study, as will clinic staff when outpatient studies are performed. Topics to review during information sessions should include the purpose of the study, the subject population, required procedures, and data documentation. The importance of protocol adherence and the collection of necessary data should be stressed to all personnel.

To inform your colleagues about the study, consider scheduling a presentation at grand rounds or similar meetings. Sponsors will often provide study information as a PowerPoint™ presentation on a DVD or flash/thumb drive that can be used at presentations. Give colleagues and personnel working with the target population a written summary of the study or a pocket reference card that includes information on how to contact the PI and CRC when questions arise, or when they want to refer a potential subject.

You may want to develop study materials in addition to those supplied by the sponsor. A review of subject data forms should identify data that are not routinely collected or documented at your site. These might include laboratory samples required at unusual times, or requirements for physical assessments that differ from those routinely gathered by site clinicians.

For some studies, creating a form to collect source data will help staff obtain the required information without significantly increasing their workload. Source data forms will help ensure that protocol-designated procedures are performed and completed appropriately, especially important when study procedures fall outside the routine. A telephone or pager number of the person to be contacted when questions arise outside of work hours should be available to site personnel. You should review these forms with pertinent staff at the study training sessions.

Figure 11.7 Sample Source Data Form



Source Data Form

HEAT
Hypothetical Example of A Trial

Subject Name: _____ Study Number: __ __ __ - __ __ __

Time study product dose started: __ __ / __ __ __ / __ __ __ __ (day / month / year) __ __ : __ __ (00:00 to 23:59)

Timepoint	Study Test or Procedure
Before start of study product: __ __ / __ __ __ / __ __ __ __ (day / month / year) __ __ : __ __ (00:00 to 23:59)	☐ Platelet count/aPTT ☐ CBC/Chemistry panel ☐ 12-lead ECG ☐ BP _____ /_____ Pulse _____
12 hours after start of study product: __ __ / __ __ __ / __ __ __ __ (day / month / year) __ __ : __ __ (00:00 to 23:59)	☐ Platelet count/aPTT ☐ 12-lead ECG ☐ BP _____ /_____ Pulse _____
24 hours after start of study product: __ __ / __ __ __ / __ __ __ __ (day / month / year) __ __ : __ __ (00:00 to 23:59)	☐ Platelet count/aPTT ☐ CBC/Chemistry panel ☐ 12-lead ECG ☐ BP _____ /_____ Pulse _____ ☐ Physical exam

_____
Signature of person recording data

__ __ / __ __ __ / __ __ __ __ (day / month / year)
Date

For questions regarding the HEAT protocol call 123-555-6789 or page 123-555-0000

A record of training and education sessions should be kept as part of your study file. This should include general clinical trials training and Good Clinical Practice training for the PI, CRC, and other study personnel, as well as trial-specific training.

Begin Randomization and Enrollment of Subjects

Subject enrollment can begin once the site staff has been oriented to the study. A consent form signed by the subject must be obtained before initiating any protocol-required procedures, and a copy must be provided to the subject (refer to Chapter 4 for additional details on the informed consent process). Subject contact information should also be collected as soon as possible after enrollment to provide the CRC with telephone numbers/e-mail addresses to use when scheduling follow-up visits.

The method used to randomly assign the subject to a treatment may vary according to the study protocol. Many trials use a telephone interactive voice response system (IVRS), an automated system for confirming eligibility and assigning study treatment. Randomization is also done online in some studies, while others require sites to call a telephone number and speak to an individual who will confirm pertinent subject characteristics and assign a randomization strategy. The protocol should detail the randomization process and contact numbers or Web sites, and this information should be made readily available where subjects will be enrolled. Typically the PI or CRC enrolls subjects in the trial, but there are trials in which non-study personnel perform randomization.

Once the first few subjects have been enrolled, review the enrollment process to identify the components that worked well and those that were not as successful. Adjustments to the enrollment process or enrollment packet should be made as early as possible, so that a revised plan is in place to enroll subsequent subjects.

Study Maintenance Phase

After processes have been established and the first few subjects have been enrolled, you gradually move into what may be referred to as the maintenance phase of the study. During this phase, activities include the completion of subject data forms as well as continued screening and enrollment of subjects. You will need to address trial-related concerns as they arise and maintain enthusiasm for the study.

Complete Data Forms

Timely completion and submission of subject data forms are important activities during the maintenance phase. In some studies, an interim analysis is performed on data at pre-determined timepoints; major decisions, such as whether the trial should be modified or continued without changes, are based on the data reviewed in this analysis. The sponsor or data center usually provides instructions on how and when forms should be completed and submitted.

From a practical point of view, it is best to record the data as they become available. As you complete data forms for the first few subjects, you will be able to identify areas where data are not being recorded in your source documents. With this information, you can take corrective action to ensure the data are available for future subjects. Actions might include developing a worksheet to remind patient-care providers when vital signs need to be evaluated, or requesting that staff record data in a subject's medical record. Worksheets that you develop to record source data can be used as source documents if the worksheet is signed and dated by the person recording the data. Chapter 14 discusses data collection in greater detail.

Report Serious Adverse Events (SAEs) and Unanticipated Problems

The protocol or other study documents will outline SAEs that may require expedited reporting in the study. Events that require expedited reporting may vary widely from one trial to the next, so familiarize yourself with the requirements and event definitions for the specific trial. This is an important safety issue for all subjects enrolled in the study and requires vigilance on the part of participating PIs and CRCs. Detailed information regarding adverse events and unanticipated problems involving risks to subjects or others can be found in Chapter 6.

Conduct Subject Follow-up Visits

Studies that involve multiple follow-up visits over a long period of time offer a unique set of challenges to the investigative site. Visits must be planned, and tests or procedures required at the time of the follow-up visit must be coordinated and scheduled. Be aware of required study procedures for each visit so that appropriate time is allotted for tests and evaluations. The use of worksheets, checklists, and study calendars will help ensure protocol adherence; you may want to create a *Subject Visit Calculator* to help establish the date of

Figure 11.8 Subject Visit Tracking Log

Visit Tracking Log

HEAT
Hypothetical Example of A Trial

- Record scheduled date in pencil; record in ink when visit has been completed.
- Contact subject a week before scheduled visit as a reminder.
- Schedule ECG and blood samples for morning of visit.

Enrollment Visit 1 Week 0	Subj. Initials	Study Number	Randomization Visit 2 Week 1	Visit 3 Week 2	Visit 4 Week 4	Visit 5 Week 6	Visit 6 Week 8	Study Completion Visit 7 Week 12
08/JAN/2009	XYZ	001	15/JAN/2009	22/JAN/2009	05/FEB/2009	19/FEB/2009	05/MAR/2009	
17/JAN/2009	ABC	002	24/JAN/2009	31/JAN/2009	14/FEB/2009	28/FEB/2009		
02/FEB/2009	CDE	003	09/FEB/2009	16/FEB/2009	23/FEB/2009			
21/FEB/2009	PDQ	004	28/FEB/2009	07/MAR/2009				

each visit (see following page). This can easily be done in an Excel™ chart or other spreadsheet program that automatically fills in the anticipated date of visits, and can recalculate dates of future visits based on actual visit dates. For an overview of all subject visits, you may want to use a *Visit Tracking Log* listing all enrolled subjects and completed visit dates.

To facilitate the planning of follow-up visits, consider the following suggestions:

- Establish a location and times when the PI and CRC are both available.
- Confirm that protocol-required procedures, such as blood drawing or exercise testing, can be performed during the time allotted for the visit.
- Provide the subject with an appointment card or a study calendar with scheduled appointments.
- Call or send a reminder card to subjects before each appointment.
- Establish a system for tracking each subject's scheduled appointments, completed appointments, and missed or canceled appointments.
- Contact the subject by telephone when there is a long interval between visits. Ask the subject if he or she has any trial-related questions, and take the opportunity to reinforce the importance of participation in the study.

Ensure Subject Retention and Compliance

While keeping site study team members informed is critical to the success of the study, keeping enrolled subjects informed about the trial is likewise vital. Regulations regarding informed consent require the PI to keep subjects updated throughout the trial. It is thus imperative that as the trial progresses subjects are provided with information that might affect their decision to continue study participation.

After enrollment, issues such as subject retention and compliance with the protocol become central to ensuring the safety of the subject and the integrity of the study. To minimize the number of subjects who choose to withdraw from a study, the CRC will want to develop a relationship with the subject that allows open communication and encourages the subject to ask questions and voice concerns or frustrations. For example, if a subject is unhappy about a long wait during a follow-up visit to have blood tests and an x-ray done, the CRC may be able to schedule the visit at a less busy time of day.

Figure 11.9 Sample Subject Visit Calculator

Subject Visit Calculator

Use this visit calculator to project future study visits.

1. Enter the actual date and time of the Enrollment/Randomization Visit. Future study visits will be projected from the Enrollment/Randomization date and time.
2. Record the actual dates the subject is seen for study visits in the "Actual Date/Time" column.
3. If a randomization date or time is entered in error, enter the correct date or time and press enter. The field will automatically be populated with the new information.
4. For each subject, save the calculator as a separate file. Maintain the spreadsheet electronically or print out once the projected dates are populated.

Day 0 Enrollment/Randomization	Actual Date/Time 9/1/2009 12:00 PM	
Visits	**Projected Date/Time**	**Actual Date/Time**
Day 1	**Between** 9/2/2009 10:00AM **and** 9/2/2009 2:00PM	
Day 2	**Between** 9/3/2009 10:00AM **and** 9/3/2009 2:00PM	
Day 3	**Between** 9/4/2009 10:00AM **and** 9/4/2009 2:00PM	
Day 4	**Between** 9/5/2009 10:00AM **and** 9/5/2009 2:00PM	
Day 5	**Between** 9/6/2009 10:00AM **and** 9/6/2009 2:00PM	
Day 6	**Between** 9/7/2009 10:00AM **and** 9/7/2009 2:00PM	

If the blood tests are done with the subject fasting, some light refreshments provided immediately after the tests are completed may resolve the matter.

Making sure that subjects return for follow-up visits is particularly important. Sending visit reminders, telephoning subjects between visits, and providing a subject newsletter can all help to maintain subjects' interest in a study. Reminding subjects of what to expect during each visit (time commitment, blood draws, special tests, etc.) will help foster cooperation and minimize frustration. If necessary, establish special clinic hours (during the lunch hour, or before or after work) to maximize subject compliance. Establishing a positive and helpful relationship with study participants will be invaluable in gaining full cooperation and ensuring that subjects complete the full course of study therapy.

To facilitate subject retention:

- Explain the study procedures and length of commitment thoroughly at time of enrollment and repeat at the first follow-up visit.
- Discuss visit frequency and approximate time commitment for the study.
- Discuss and solve transportation issues (provide parking vouchers, explore public transportation, offer community/home research visits if possible).
- Involve the subject's family in discussions.
- Establish good communication with the subject's primary care physician/referring physician.
- Provide subjects with easy-to-carry (e.g., wallet card) and easy-to-understand study instructions (e.g., how and when to take study medication, storage requirements, other medications to avoid, restricted foods).

Subject Discontinuation or Withdrawal

There are a number of reasons why subjects may not continue a study through to completion. Some may be related to a subject's personal unwillingness to continue, while others could be caused by medical issues. Medical reasons for withdrawal might include an SAE, deterioration of the subject's health, pregnancy, or an abnormal laboratory value that represents an intolerable adverse effect (e.g., an elevated creatinine or significant decrease in hemoglobin).

In some cases, subjects must be withdrawn because of noncompliance with study medication or procedures, or if concomitant medications prohibited by the protocol were taken. During a study with long-term follow-up, withdrawal may be necessary when a

Figure 11.10 Sample Subject Contact Information Form

Protocol-Study #: ___ ___ ___ – ___ ___ ___ (protocol number / site number) Subject's Initials: ___ ___ ___ (first middle last)

HEAT
Hypothetical Example of A Trial

Contacts

Subject Contact Information (please print)

Subject Identification

Subject name: _____, _____ _____ (Last, First, Middle)

Resident identification number: _____ **Medical record number:** _____

Primary home address: _____

_____

_____

Primary home phone number: _____ → Best time to call: _____ ☐ AM ☐ PM

Business phone number: _____ → Best time to call: ☐ AM ☐ PM

E-mail address: _____

Spouse or significant other: _____, _____ _____ (Last, First, Middle)

Spouse/significant other business name: _____

Spouse/significant other business phone number: _____

E-mail address: _____

Secondary Residence (vacation home, etc.)

Mailing address: _____

_____

_____

Phone number: _____ → Best time to call: _____ ☐ AM ☐ PM

Alternative Contacts *(please list two relatives, friends or neighbors **not living with** subject)*

1 Name: _____, _____ _____ (Last, First, Middle)

Relationship to subject: _____

Mailing address: _____

_____

_____

Phone number: _____ → Best time to call: _____ ☐ AM ☐ PM

E-mail address: _____

2 Name: _____, _____ _____ (Last, First, Middle)

Relationship to subject: _____

Mailing address: _____

_____

_____

Phone number: _____ → Best time to call: _____ ☐ AM ☐ PM

E-mail address: _____

Local/Referring Physician or Primary Care Physician/General Practitioner

Name: _____, _____ _____ (Last, First, Middle)

Mailing address: _____

_____

_____

Physician's office phone number: _____ **Office fax number:** _____

Contains confidential subject information. Do NOT fax or send this page with subject's case report form.

subject moves to a location where the required follow-up visits/tests/procedures cannot feasibly be performed.

Most of the reasons for withdrawal listed above are out of the control of the PI and CRC. However, there are a number of other reasons for study withdrawal that they may be able to address. Over time, subjects may lose interest in a study or feel as if they are spending too much time at their follow-up visits. They may feel that they are being treated like "guinea pigs," or it may be difficult to get to their appointments because of transportation problems or work responsibilities. The PI and CRC can address some of these issues using the following measures:

- Always treat subjects with respect.
- Make sure subjects are treated in a way that shows their participation is important.
- Schedule appointments to minimize waiting time.
- Schedule subjects to be seen by the same CRC at visits, when possible.
- Give subjects time to discuss how they feel.
- Make sure subjects feel comfortable to ask questions.

In spite of the best efforts of the CRC and PI, some subjects will still decide to withdraw from study participation. If this happens, you can ask the subject if he or she is willing to allow limited access to medical information that will provide endpoint information such as hospitalizations or emergency room visits. Obtaining permission to collect this type of information will contribute to the final analysis of the data.

Subjects Who Are Lost to Follow-up

There may be times when you will be unable to locate study subjects when follow-up is required. Some subjects decide not to continue study participation but do not inform the CRC or PI of their decision. Subjects may also miss visits because of other illnesses resulting in hospitalization, or personal circumstances such as a change in family dynamics. The CRC should determine that the subject is lost to follow-up only when the subject does not show up for scheduled visits and repeated attempts to contact the subject have failed.

The absence of data from subjects lost to follow-up affects the statistical analysis and may require the enrollment of additional subjects. Therefore, every attempt should be made to locate all subjects. Use the contact information obtained at the time of enrollment to identify a friend or relative not living with the subject, or the physician responsible for the subject's ongoing care, who

may know the subject's whereabouts. Suggestions for locating subjects include:

- Call at various times during the day, at home or work, over the course of several weeks.
- Contact the primary or referring physician.
- Contact the individual not living with the subject listed on the subject contact information form.
- Review hospital medical record/emergency contact/next-of-kin information.
- Call the local telephone company directory information.
- Send a certified letter to the subject and/or the individual not living with the subject.

In some situations you may be able to visit the subject's home or community to attempt to locate the individual. You should document each attempt at contact; at the end of the study you may be asked to make additional attempts to establish contact or determine if the subject has moved or died.

Unblind Study Treatment Only When Required

The underlying philosophy for unblinding study treatment is that it should occur only when knowledge of the treatment code will influence decisions about subject care. More often, the unblinding of study treatment is not necessary, and the appropriate decision for subject management is to discontinue the study drug, reduce the dose, or temporarily stop study drug as indicated in the protocol. Unblinding study treatment rarely adds further information that affects subject care.

Studies that are blinded to both the investigator and the subject must provide a mechanism to unblind study medication in the case of an emergency in which it is essential to know what study treatment the subject received. Methods for unblinding include: 1) calling a specific number with 24-hour availability; 2) envelopes containing the subject treatment information that may be kept in a secured location at the site; and 3) scratch-off or wipe-off labels on the study drug containers. The PI is typically required to obtain permission from the sponsor or medical monitor before unblinding can occur. Instructions about the appropriate unblinding procedure for the study will be provided in the protocol, by the sponsor, or by the designated study pharmacy.

Maintain Study Drug/Device Accountability

Meticulous records of dispensing study drug/devices must be maintained as dispensing and use occurs. Accountability records are usually provided by the study sponsor and should be completed at the time you dispense the investigational products. When unused study drug is returned by subjects, careful counting and recording is required to account for all medication. Accountability records will also provide a place to record the details of test products returned to the sponsor for any reason (e.g., expired product, end-of-study, and device malfunction) or destroyed.

Manage Specimens, Samples, and Other Study-related Materials

Many clinical trials require special handling, labeling, and processing of samples and tissues. The protocol should provide you with all the information necessary to manage these activities. Samples may need to be processed and/or shipped to a central laboratory, may need to be labeled in a blinded manner identifying the study and timepoint (e.g., 6 hours after study drug infusion), or kept on-site in specific environments (e.g., stored at −70 degrees Celsius). You may need to ship samples to a core lab on dry ice in special containers, necessitating a source for dry ice at your institution. In some trials, the films or reports from x-rays, scans, or other procedures may need to be sent off-site to be evaluated by an independent reviewer. For behavioral studies, you may have audio and/or video files that must be labeled in a specific manner and sent off-site for review. In all cases, it will be essential to label items carefully and exactly as instructed by the sponsor or core lab, and items must be shipped at the specified intervals.

Obtain Answers to Urgent Clinical Questions

Many studies have a "helpline" telephone number where clinicians are on call 24 hours a day to assist in making clinical decisions regarding potential subject eligibility, or in managing urgent clinical problems for study subjects. Typically, questions posed to the helpline should be urgent and about real subjects, not hypothetical situations. Additional contact numbers are generally provided for non-urgent study-related questions, such as those regarding completion of data forms.

Continue Communication

You should maintain regular meetings and communication within your study team to ensure that the study is progressing as planned,

by discussing subject accrual and retention, SAEs, and protocol amendments. If recruitment is slower than expected, you should discuss strategies to identify additional subjects. Any issues or concerns should be raised with the study team for discussion and problem-solving.

During this phase of the study you will be in contact with the monitor and/or site management team designated by the sponsor. Regular communication with the monitor serves to update the site regarding overall study progress, relays helpful information, and allows checking of the status of data forms. Sharing this information with appropriate personnel at your site can help to maintain their enthusiasm for the study.

Some sponsors may provide electronic newsletters or e-mails to provide new information about the study and provide helpful suggestions to all sites. Sponsors often create a study-specific Web site to facilitate communication; some provide public access to help keep subjects informed of the trial's progress.

Maintain Study File

Throughout the course of the study, the site study file must be kept up-to-date. Communications, reports, and other pertinent information should be filed on an ongoing basis throughout the study. Refer to Chapter 12 for further information on study documents.

Study Completion and Close-Out Phase

Eventually, subject recruitment will be complete and the sponsor will begin the process of closing out trial enrollment at participating sites. Many trial-related activities continue after recruitment has been completed, including recording and submission of subject data. Follow-up visits often must be scheduled after completion of enrollment, and subject care issues may still surface. The final study close-out process may be performed during an on-site monitoring visit, or may take place via telephone, Internet, or by fax, with the use of checklists to ensure that all activities have been completed.

Studies may be terminated for reasons other than the completion of subject recruitment. When an interim safety analysis reveals data indicating that one treatment is significantly more beneficial than other treatment arms, a study will be stopped, as it would be unethical to continue randomization into the non-beneficial treatment arms. Or the reverse may be true – the treatment under investigation may be more harmful than anticipated and therefore

unsafe to continue in the trial. Sometimes it becomes clear over time that sites will not be able to meet the subject enrollment target and the overall trial is stopped for that reason.

However, whatever the reason for the end of the study, close-out procedures must be completed. The following list identifies general activities that must be performed at study's end; sponsors may require additional activities, depending on the type of study and product under investigation.

Completion of All Subject Data Forms and Resolution of Data Queries

All outstanding subject data forms must be completed and submitted. Data queries generated by the CRA or computerized checks must be answered and resolved.

Destruction or Return of Study Materials

The protocol will usually specify what happens to study materials at the end of the study. Accountability forms must be completed and study drug counts reconciled with the remaining drug. Return or destruction of the test product must be documented and the records kept in the site study file. If there are any questions, check with the sponsor before returning or destroying the study materials or test products.

Review of Site Study File

If the CRA performs an on-site close-out visit, the CRA will check the site study files for completeness. Documents should be filed in chronological order and correctly signed and dated. A note to the file should be written to explain any missing documents. It will be helpful to use a checklist provided by the sponsor/designee, or one that you have developed for your site, to ensure that all items have been completed and filed.

Submission of the Final Report

The final report should document the study completion, incorporating an enrollment summary including subjects withdrawn and dropped out, plus any SAEs not yet reported. IRBs may require the final report to be in a specific format; check with your IRB to determine what information you are required to include.

Long-term Storage of Study Records

Record retention regulations in 21 CFR 312.62(c) and guidelines in ICH E6 section 4.9.5 require essential documents of a study to be retained for a minimum of 2 years after the approval of a marketing application; if no marketing application will be submitted, records must be kept for 2 years after the investigation of the product is discontinued. Institutions, IRBs, and sponsors can require a longer record retention period than stated in the regulations. For example, an IRB might request that in a study in which young children were subjects, the records are kept until all subjects have passed the age of 21 years. It is the sponsor's responsibility to notify investigators as to when study documents are no longer needed and can be destroyed; however, investigators must be sure to also fulfill the record retention requirements at their site.

Long-term Storage of Study Files

Label boxes:
- Name of PI
- Address of Study Site
- Contact information
- "Study Files for Trial XX"
- "ABC Pharmaceutical Company"
- Sponsor contact information
- DO NOT DESTROY CONTENTS OF THIS BOX

Records should be carefully stored in boxes labeled with information describing the contents. Ideally, the label on the box should state the PI's name and contact number, the name of the clinical trial and sponsor, and a warning such as DO NOT DESTROY CONTENTS OF THIS BOX. If study files are kept in an off-site location, information should be kept in the PI's office indicating the location of study files. You may need to discuss who will pay for off-site storage with the sponsor; if there is a reason that files cannot be stored at the site, contact the sponsor on how best to handle storage. Always contact the sponsor before destroying study files. You must ensure that the study records are properly disposed of in a manner that maintains privacy and confidentiality.

On-going communication with the sponsor, the CRA, and the site study team is crucial during the close-out phase. Provide feedback to site personnel and study staff in other departments, such as the pharmacy and labs, who participated in the study. When study results are released or published, share this information with the staff at your site, including nursing and pharmacy personnel, laboratory staff, and others who worked with study subjects and performed study procedures. This not only provides the trial results to the many personnel who participated in the study, but also helps to acknowledge their contributions. You may also want to share the results with study subjects who have expressed an interest in learning the outcomes of the trial.

Figure 11.11 Checklist for Close-Out

HEAT
Hypothetical Example of A Trial

Sample Study Close-out Checklist

Site# __ __ __

Review your study file and confirm that all items are present.

1. Protocol/Amendment(s)
   - ❑ Protocol and Signature Page (Investigator's Agreement) dated May 30, 2008
   - ❑ Protocol amendment dated February 19, 2009
2. Investigator's Brochure/Safety Alerts/Data Safety Monitoring Board (DSMB)
   - ❑ Investigator's Brochure dated February 19, 2008
   - ❑ Safety Alert #1004 dated January 19, 2009
   - ❑ DSMB Letter dated May 26, 2009
3. IRB Approved Consent Form(s) and Expiration Date (if applicable)
   - ❑ Version_____dated___/___/___ expiration ___/___/___ or ❑ NA
   - ❑ Version_____dated___/___/___ expiration ___/___/___ or ❑ NA
4. IRB Approval Letter(s)
   - ❑ Protocol version dated May 30, 2008
   - ❑ Protocol amendment dated February 19, 2009
   - ❑ Consent form dated May 30, 2008
   - ❑ Consent form dated February 19, 2009
   - ❑ Recruitment advertisements dated May 30, 2008
   - ❑ Office advertisement posters dated May 30, 2008
   - ❑ Patient newsletter dated December 15, 2008
5. IRB Communications
   - ❑ IRB membership roster(s)
   - ❑ Annual IRB progress report
   - ❑ IRB notification of serious and drug related events; protocol violations/deviations
   - ❑ Other: _____
   - ❑ Final report submitted to IRB: ___/___/___ to sponsor: ___/___/___
6. Form FDA 1572 / Site Signature and Delegation Log
   - ❑ Form FDA 1572 signed ___/___/___
   - ❑ Revised Form FDA 1572 signed ___/___/___
   - ❑ Site Signature and Delegation Log
7. Annual Financial Disclosure and Conflict of Interest Forms
   - ❑ Principal Investigator
   - ❑ Sub-Investigator or ❑ NA
8. Curriculum Vitae (CV) and Medical License
   - ❑ Principal Investigator license expiration date ___/___/___
   - ❑ Sub-Investigator or ❑ NA license expiration date ___/___/___
9. Laboratory Certifications
   - ❑ Clinical Laboratory Improvement Amendment (CLIA) expiration date:___/___/___
   - ❑ College of American Pathologist (CAP) expiration date:___/___/___ or ❑ NA
   - ❑ Laboratory normal ranges
10. Study Drug Records
    - ❑ Study Drug Packing Invoice
    - ❑ Dispensing Logs
    - ❑ Study Drug return forms
11. Training for Key Site Personnel
    - ❑ Human subject protection training
    - ❑ Investigator Meeting attendance certificates
    - ❑ Electronic data capture training
12. Study Logs
    - ❑ Screening Logs
    - ❑ Confidential Master Subject Logs
    - ❑ Site Visit Log(s)
13. ❑ Study Correspondence

Planned storage area for subject data records: _____

Planned storage area for subject consent forms: _____

Planned storage area for financial contracts: _____

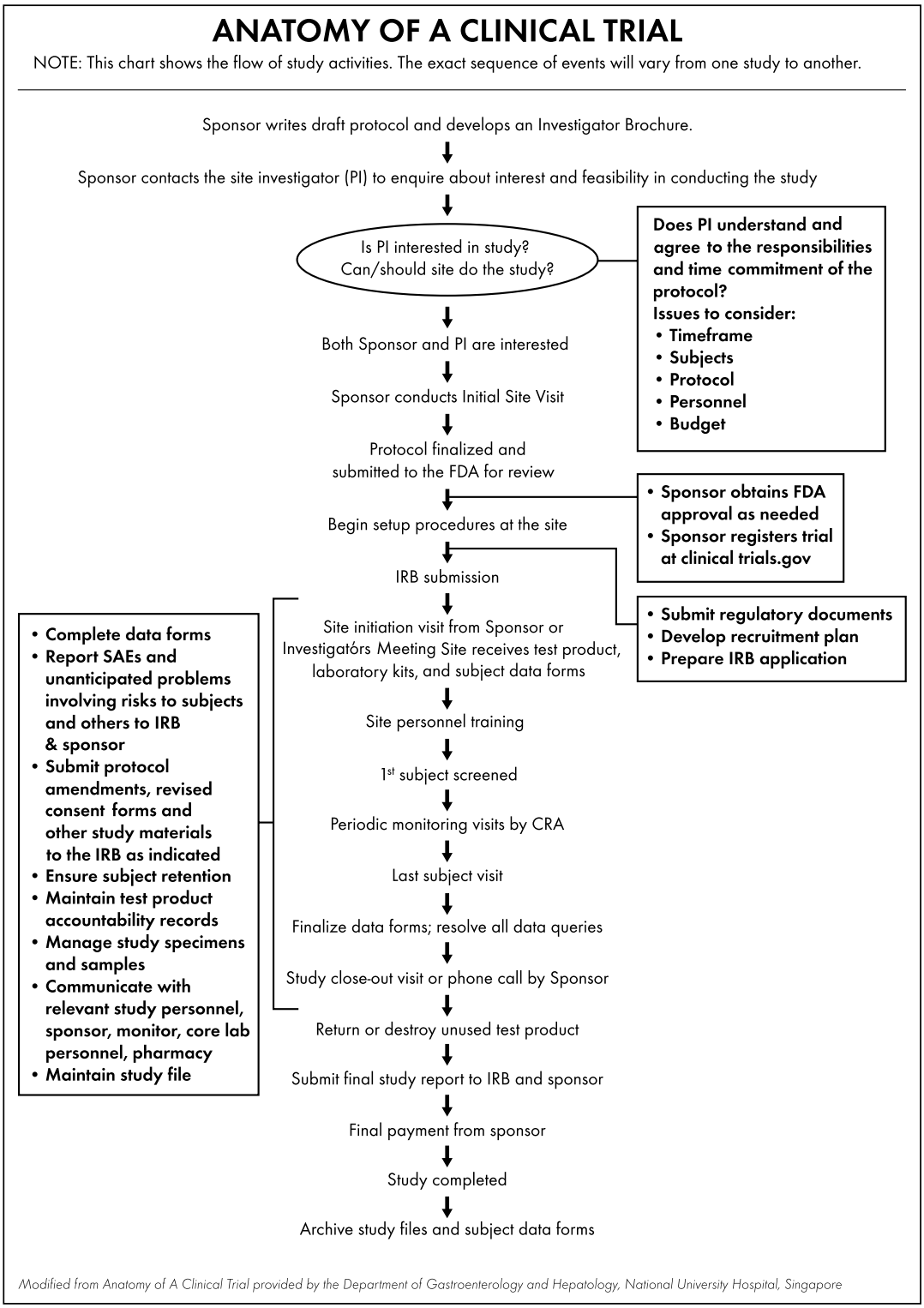
Planned storage area for study files: _____

_____ _____

Print Name of Principal Investigator Signature of Principal Investigator

Date:_____

Figure 11.12 Anatomy of a Clinical Trial



Modified from Anatomy of A Clinical Trial provided by the Department of Gastroenterology and Hepatology, National University Hospital, Singapore

12 Study Documents/ Essential Documents

In this Chapter

- The documents you'll need to keep throughout the trial, from start-up to close-out
- How to organize and maintain your site study file

"In dwelling upon the vital importance of *sound* observation, it must never be lost sight of what observation is for. It is not for the sake of piling up miscellaneous information or curious facts, but for the sake of saving life and increasing health and comfort."

Florence Nightingale (1820–1910), Pioneering Nurse and Statistician

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

One of the major activities usually performed by the Clinical Research Coordinator (CRC) is the management of the many documents used in a clinical trial. These study documents ensure accountability by Principal Investigators (PIs), sponsors, monitors/clinical research associates (CRAs), and institutional review boards (IRBs). Many are required by regulatory authorities, while others may be unique to an individual sponsor or IRB and therefore not used in all trials. There are also documents that are specific to drugs and biologics trials and others that may be used only in device trials.

Essential Documents for the Conduct of a Clinical Trial

Essential documents are those "documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced" (ICH E6: Glossary 1.23). These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all regulatory requirements.

The PI and CRC will find information about these documents spread throughout the Code of Federal Regulations (CFR) used by the U.S. Food and Drug Administration (FDA), whereas the International Conference on Harmonisation (ICH) E6 guidance for Good Clinical Practice (GCP) summarizes these documents in one section and refers to them as "essential documents." You may choose to organize your study file in the same order as that in ICH E6, which groups documents by the phases of a study, or you may choose to separate your documents according to categories such as regulatory documents, administrative documents, and subject files. Some sponsors provide sites with binders or folders to use as a system to maintain your study files. No matter what method you use to organize your files, it is important that you are consistent in the method you use for filing your documents, and that your system allows you to keep your file current and complete.

You should create a study file at the onset of trial discussions and negotiations, as soon as you have any trial-related documents. This is useful for keeping track of your documents, as well as when the sponsor, CRA, and/or regulatory authorities conduct monitoring visits, audits, and inspections at your site and need to review your study file. Your file should contain all study documents relevant to the trial with the exception of the *Contractual Agreement*, which is the financial contract that outlines payment from the sponsor; this agreement should be kept in a separate file as it is not subject to review, audit, or inspection.

Documents at Study Start-Up

Many factors, including the sponsor and the type of trial, determine the order in which your site receives and completes documents. For this reason, documents may vary from one trial to another. The following list includes documents that are required by regulations,

as well as some documents that are not required by regulations but are often requested by individual sponsors. A copy of each document should be kept in your study file.

Confidentiality Agreement

When approached about participating in a clinical trial as a PI, the investigator may have to sign a *Confidentiality Agreement* before being given a copy of the protocol to review. This agreement between the PI and the sponsor requires the PI to keep confidential the contents of the protocol and any other proprietary information regarding the study. Once the Confidentiality Agreement has been signed, the PI will receive a protocol to review.

Signed Protocol and Applicable Amendments

To document the agreement between the PI and the sponsor for the PI to participate as an investigator in the study, the initial protocol and applicable amendments must be signed and dated by the PI on their respective signature pages. This serves as documentation between the PI and the sponsor that the PI will participate as an investigator in the study. A copy of the protocol plus amendments must be kept in the study file. When amendments to the initial protocol are included, you will need to provide a copy to applicable groups or individuals. For example, in an investigational drug study, you should provide a copy of the amendment to the pharmacy; document this in a memorandum to your study file, noting the date the amendment was provided. After reviewing and signing the protocol to indicate agreement to participate in the trial, additional documents will be sent to the PI.

Letter of Agreement

The *Letter of Agreement* is a contract between the investigator and the study sponsor. The details of the contract are sometimes spelled out in a formal "Letter of Agreement" or may be a copy of the "Signature Page" of the protocol, which requires signatures from both a sponsor representative and the investigator. By signing the Protocol Signature Page or a Letter of Agreement, you are promising the sponsor that you will conduct the study according to the design of the protocol and in accordance with the regulations governing clinical research.

Investigator Commitments on the Form FDA 1572

The investigator must:

- conduct the study according to the relevant, current protocol and only make protocol changes after notifying the sponsor except when necessary to protect subjects;
- personally supervise the study;
- inform subjects that the study drugs are investigational and ensure compliance with regulatory requirements for informed consent and IRB review and approval;
- report adverse experiences to the sponsor;
- read and understand the information in the Investigator's Brochure;
- ensure that all colleagues and study team members are informed about their obligations in meeting these clinical research commitments;
- maintain adequate and accurate records, and make records available for inspection;
- ensure that the IRB responsible for the review and approval of the study meets IRB regulatory requirements; agree to promptly report to the IRB all changes in research activity and unanticipated problems involving risks to subjects or others; agree to not make changes to the research without IRB approval, except when necessary to eliminate immediate hazards to subjects;
- agree to comply with all regulatory obligations for clinical investigators.

Investigator's Brochure

Along with the protocol, the sponsor will provide the PI with an *Investigator's Brochure*. This document provides the scientific rationale and background for the study; pharmacology, toxicology, and pharmacokinetics data; safety and effectiveness data; and adverse events (AEs) identified in previous pre-clinical and clinical studies. A copy of the Investigator's Brochure must be provided to your IRB and to the pharmacy (when applicable); a copy must be kept in your site study file as well.

Curriculum Vitae (CV)/Statement of Investigator Qualifications

CVs and/or other documents that show the training and qualifications of the PIs and subinvestigators are required by the sponsor. Some sponsors also ask for CVs (or résumés) and training records for all study personnel at the site.

Medical Licensure Form

Sponsors may require the current medical license numbers for the PI and subinvestigators. Sponsors may request a photocopy of the PI's medical license or may provide a *Medical Licensure Form* on which to record this information. If the study involves a controlled substance, investigators involved in the study must provide a copy of their Drug Enforcement Administration (DEA) license.

Form FDA 1572

The Form FDA 1572 must be completed and signed by the PI participating in a clinical trial being conducted under an Investigational New Drug (IND) application. The investigator's signature indicates his or her commitment to complying with the statements in section 9 of the Form FDA 1572. These statements commit the PI to follow the protocol, personally supervise the study, report adverse events, maintain records, and comply with IRB requirements and informed consent regulations. The Form FDA 1572 with the **original** signature will be collected by the sponsor and is ultimately submitted to the FDA by the sponsor with the marketing

Figure 12.1 Sample Medical Licensure Form

Site #: _ _ _ _ _

HEAT
Hypothetical Example of A Trial

MEDICAL LICENSURE INFORMATION

Institution: _____

City and State/Province: _____

This form needs to be submitted in its entirety. The Principal Investigator must be the same name as in section 1 of the Form FDA 1572.

Principal Investigator's Name	Medical License Number	Board Specialty	Board Certification Number

If you have a Co-Investigator his/her name and address must appear in section 1 of the Form FDA 1572 along with the Principal Investigator. (Please note: both PI and Co-PI must sign the Form 1572.) Subinvestigators must be listed in section 6 of the Form FDA 1572.

Subinvestigator's Name	Medical License Number	Board Specialty	Board Certification Number

application. When changes need to be made to Form FDA 1572, a new form must be completed and submitted; correction fluid and correction tape may not be used to make changes on the form.

The Form FDA 1572 is used in clinical trials of drugs and biologics; there is no equivalent form for device trials. Instead, sponsors ask investigators to sign an *Investigator Agreement* that commits the PI to similar responsibilities as those listed on the Form FDA 1572. Device regulations in 21 CFR 812.43(c) require sponsors to obtain a signed agreement from each PI including the PI's CV, a statement of

the PI's relevant experience, explanation of circumstances leading to the termination of other research (if applicable), and a statement of the PI's commitment to:

1 Conduct the investigation in accordance with the agreement, the investigational plan, applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA;
2 Supervise all testing of the device involving human subjects; and
3 Ensure that the requirements for obtaining informed consent are met.

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 21 CFR 54. 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. [21 CFR 312.64(d) and 21 CFR 812.110(d)]

Financial Disclosure Information

Regulations require sponsors to collect financial disclosure information from each investigator participating in a clinical study of drugs, biologics, and devices. For investigational drug studies, this information must be collected from each investigator listed in sections 1 and 6 of the Form FDA 1572; for device studies, disclosure information must be provided for investigators listed in the Investigator Agreement. The disclosure of financial interest in the sponsor organization or in the product being investigated applies to the investigators, their spouses, and their dependents. Refer to Chapter 3 for additional information about financial disclosure.

IRB Approval

The first step in initiating a study at your site is submitting the protocol, Investigator's Brochure, and consent form to the IRB for approval, usually accompanied by a completed submission form specific to your IRB. If the sponsor supplies a sample consent form, you must customize the consent form with local names and contact information before submitting it to the IRB. After the consent form has been modified to suit your site, approval of the draft informed consent form must be obtained from the sponsor before you submit the modified consent form to your IRB. After receiving sponsor approval of any subject recruitment materials and advertisements that you have created, these must also be submitted and approved by the IRB before use. The IRB will review the study documents and may ask questions about the study, request additional information, or ask for revisions to be made to the consent form, advertisements, or other materials before approving them.

IRB Approval Letter

When the IRB approves a study, it must provide the PI with a letter documenting approval to conduct the study at the site. The IRB letter

should specifically state the name and date of the protocol and the protocol version number. Written IRB approval of advertisements and subject educational materials must also be provided. The IRB usually includes specific instructions in the approval letter, including the time period of approval and the frequency of expected reporting to the IRB. Approval for the protocol, the consent form, and other applicable documents such as advertisements and assent forms are often included in a single letter; however, they may also be provided in separate letters. Some IRBs indicate consent form approval with a stamp and date on a blank copy of the consent form. The PI should submit a copy of the IRB approval letter to the sponsor and keep the original in the site study file.

An example of an IRB letter indicating study approval can be found on the following page. Make sure your IRB approval letter includes:

- The protocol name and version
- Approval for the protocol
- Approval for the consent form
- Approval for advertisements and subject materials
- Date of IRB approval
- Date of approval expiration
- Signature of IRB chairperson or designee.

As part of your site regulatory files, IRB approval letters will be reviewed during on-site monitoring visits and may also be reviewed by auditors during an audit and the FDA during a site inspection.

IRB Membership Documentation/Assurance

The site study file should also include a list of all IRB members. In some cases, IRBs do not allow the members' names to be given out and will instead supply a statement that the IRB meets and complies with all relevant regulations. When this is the case, submit the statement to the sponsor and keep a copy in your study file.

Institutions receiving federal funding for clinical trials must have a current written assurance stating that the institution and IRB will comply with the human subject protection regulations in 45 CFR 46.103.

If the PI, subinvestigator, or CRC is a voting member of the IRB, documentation that he or she was not involved in voting for IRB approval for the designated study should be recorded and kept in your study file. The IRB will keep a copy of this documentation in their files as well.

Figure 12.2 Sample IRB Approval Letter

INSTITUTIONAL REVIEW BOARD
1212 Seventh Avenue, SW • Anywhere, US 12345-6789
P.O. BOX 12345 • Anywhere, US 12345-6789
(123) 456-7890 • 1-800-123-7890 • FAX (987) 654-3210

July 18, 2009

Dr. Candoit
Clinical Research Site
Anywhere, US 12345

Subject: Approval for HEAT Study: Hypothetical Example of A Trial
Sponsor Protocol Number: 123 IRB Protocol Number: 12345

Dear Dr. Candoit:

On July 18, 2009, the Institutional Review Board (IRB) Panel 2 reviewed:

- The above-referenced protocol
- Associated consent form template version 1.0 dated June 30, 2009
- Advertisement #12345.0 Information for patients considering participation in HEAT—As Submitted
- Advertisement #12346.0 Do you have moderate to severe hot flashes?—As Submitted
- Clinical Study Diary #12347.0—As Submitted.

The Board has determined the research to be in compliance with applicable requirements of Federal Regulations 21 CFR 56, 45 CFR 46, and ICH. Consequently, the board voted to find the protocol, consent form template, and associated materials approved.

Study approval expires: July 18, 2010
Please submit renewal information at least 30 days prior to expiration.

Ima Chairperson
Ima Chairperson, MD
Chair, Institutional Review Board

IRB-Approved Consent Form

The consent form – including assent forms for children, the "short form" version of a consent form, and the written summary that corresponds to the short form – should be submitted to the IRB for approval with the protocol. Approval of the consent form may be stated in the IRB letter approving the protocol, or the consent form itself may be stamped "approved" and dated and initialed by the IRB

chairperson. Verification that the consent form was approved by the IRB should be forwarded to the sponsor.

Check with your site's medical records department to ensure that the consent form meets your hospital's or institution's archiving specifications. Signed consent forms that are kept in the subject's medical record are sometimes discarded by the medical records department if not printed on institution letterhead or approved by the institution's internal forms committee. Keep the original signed consent form in your site study file and place a copy of the consent form in the subject's medical record or clinic chart.

IRB-Approved Advertisements and Subject Materials

IRBs must approve all advertisements and subject materials before use. Subject materials include those provided by the sponsor, such as subject diaries and questionnaires, and materials that provide subjects with study-specific and disease-specific information, such as educational pamphlets and posters. A copy of all materials approved for use should be kept in your study file.

Laboratory Certification and Normal Ranges Form

When laboratory samples are processed at your institution or a local laboratory and the results are recorded on the data forms, the sponsor may require a copy of the certification indicating that the laboratory meets the current standards for handling and processing samples. Laboratory certification is required under the Clinical Laboratory Improvement Act of 1988 (CLIA) and is usually issued by the College of American Pathologists (CAP). When the sponsor requires proof of certification, copies of the certificates should be obtained from all laboratories that will process samples included as part of the subject data. Certification is performed by the state (and sometimes the city) where the laboratories are located, and usually covers a 2- to 3-year period. Be sure to obtain a copy of the renewal letter or certificate if the laboratory certification expires and is renewed during the study period. Some sponsors may also request a copy of the laboratory director's license and CV.

In many trials, a *Laboratory Normal Ranges Form* must be completed, providing normal ranges for the laboratory results recorded on the subject data forms. This provides a reference for comparing the reported subject values. If these ranges change during the trial

Figure 12.3 Sample Lab Normals Form

Lab Normals Form

HEAT
Hypothetical Example of A Trial

(Lab use only) Lab ID: _____

Site #: _____ Lab Name: _____ Date: ␣␣␣␣ year ␣␣ month ␣␣ day

Normal Ranges for Laboratory Data

HEMATOLOGY	Units	Range: Low	Range: High
Hemoglobin			
Hematocrit			
MCV			
Quantitative platelet count			
WBC			
Differential:	**Units**	**Low**	**High**
Neutrophils *(including bands)*			
Lymphocytes			
Monocytes			
Eosinophils			
Basophils			
Atypical lymphocytes			
Other: _____			
Other: _____			
Other: _____			
Remaining cells			

BIOCHEMISTRY	Units	Range: Low	Range: High
Na^+			
K^+			
HCO_3^-			
Urea			
BUN			
Creatinine			
Total calcium			
Inorganic phosphate			
Uric acid			
Total bilirubin			
Alkaline phosphatase			
ALT (SGPT)			
AST (SGOT)			
Albumin			
Total protein			
Glucose			
LDH			

Changes to Normal Ranges

Did the units or normal ranges change at any time during the trial *(e.g., change in test method)*? ◯ Yes ◯ No

If Yes, please record changes to normal ranges below:

Lab Test	Units	Range: Low	Range: High	Date Changed
				␣␣␣␣ year ␣␣ month ␣␣ day
				␣␣␣␣ year ␣␣ month ␣␣ day
				␣␣␣␣ year ␣␣ month ␣␣ day
				␣␣␣␣ year ␣␣ month ␣␣ day
				␣␣␣␣ year ␣␣ month ␣␣ day
				␣␣␣␣ year ␣␣ month ␣␣ day

due to new laboratory equipment, recalibration, or other reasons, updated ranges should be collected and provided to the sponsor, with a copy kept in your site study file.

Site Demographics Form

Also called a *Site Information Sheet*, this form provides the sponsor with the names, telephone numbers, shipping addresses, and e-mail addresses of trial-related personnel, as well as other general information about your site. This information identifies where and to whom correspondence, test products, and study materials should be shipped. It is important to update this information when names, numbers, and/or addresses change during a study. Site information is often managed electronically by the sponsor allowing updates to be easily made online.

Study Personnel CVs/Résumés and Training Records

Some sponsors will request copies of CVs/résumés and training records of site study personnel. The CVs should document the qualifications of the CRC and others to whom the PI has delegated study activities. Training records should indicate general education and training pertinent to clinical research and, even more specifically, to the trial. When study-specific training sessions are conducted, record a summary of the training session provided along with the date and names of attendees to document the training provided. This should be placed in the study file.

Contractual Agreement/Financial Contract

The financial contract between the PI and the sponsor identifies when and how much the site will be paid for trial-related activities. Amounts paid to sites for study participation may vary based on the actual charges and costs at different institutions and locations. The contract should specify the frequency and timing of payments, the milestones that a site must reach to generate a payment, and when final payment will be made. Budget negotiations between the PI and the sponsor should be finalized before submitting the study budget to the institution's contracts department.

Note: The financial contract should be kept separate from your study file.

Examples of Protocol Changes Requiring an Amendment:

1. An increase in the study drug dose or duration
2. A significant change in the study design (such as adding or dropping a control group)
3. The addition of a test or procedure, even when its intent is to reduce the risk of, or improve the monitoring for, an adverse event (for example, testing serum creatinine at additional timepoints if kidney function needs to be closely observed)[1]

Documents While the Study is in Progress

As a trial progresses, you will be required to submit and file additional documents. The specific documents required will depend on issues that arise during the study and may include the following:

Protocol Amendments and IRB Approval

If changes are made to the approved protocol, an amendment must be submitted to the IRB and approval obtained before the protocol changes can be implemented. Changes that require a protocol amendment in a clinical trial conducted under an IND can be found in 21 CFR 312.30. Protocol changes requiring an amendment in trials conducted under an Investigational Device Exemption (IDE) are found in 21 CFR 812.35.

Expedited Review by the IRB

While every amendment requires IRB approval, not every amendment must be reviewed by the full IRB committee to be approved. The FDA has created a list of research categories that may be reviewed by the IRB through an *expedited review* procedure. This list is published in the Federal Register and updated as needed.

An IRB may use the *expedited review* process to review either or both of the following:

1. Some or all of the research can be found on the published list of research categories that are eligible for expedited review and/or the research is found to involve no more than minimal risk, and
2. There are minor changes to a research study approved within the previous 12 months.[2]

Under an expedited review procedure, the IRB chairperson (or one or more experienced reviewers designated by the chairperson) may perform the review. The reviewers may exercise all of the IRB's authority, with the exception that they may not disapprove the study, which can only occur in accordance with a non-expedited review. The IRB must have a system in place to notify the full committee of the approval when expedited review is implemented. The IRB chairperson also has the right to request a full IRB review of any protocol amendment.

Once IRB approval for an amendment is obtained, a copy of the amendment and the approval letter must be kept in your study file and a copy of the IRB approval letter forwarded to the sponsor.

Revised Consent Forms and IRB Approval

If the original approved consent form is revised for any reason during the trial (for example, due to a safety issue or a protocol change), the revised consent form must first be approved by the sponsor and then submitted to the IRB for approval before use. This revised consent form must be used to obtain consent from all study subjects enrolled after IRB approval has been received. A blank copy of the revised consent form and all previously-approved versions must be kept in the study file. Be sure that the current version of the consent form is easily identifiable by a date and version number located on each page.

Some protocol and consent form revisions may affect subjects currently enrolled in the study, such as when additional blood tests are required, the visit schedule is changed, or study drug dosing is altered. When this occurs, all previously enrolled subjects who are still actively participating and have remaining follow-up study procedures must be informed of the changes and sign the revised IRB-approved consent form to indicate their willingness to continue participation in the study. Both the original consent forms signed by subjects as well as the revised consent forms signed by subjects must be kept in the study file; do not discard any consent forms signed by subjects.

Updated Form FDA 1572

Changes that require a new Form FDA 1572 to be completed include:

1 Changes in the investigator name or address

2 Changes in the IRB address

3 The addition of subinvestigators, local laboratories, or locations where subject visits will be conducted.

When Form FDA 1572 information is updated, a new form must be completed in its entirety, signed and dated by the PI, and submitted to the sponsor. A copy of the new Form FDA 1572 should be kept in your site study file with a copy of the initial Form FDA 1572. Note that in addition to revising the Form FDA 1572, full IRB review must also occur when the PI changes.

CVs for New PIs and Subinvestigators

When new PIs and subinvestigators participate in the study at your site, CVs must be submitted with the updated Form FDA 1572.

Updated Laboratory Certification and Normal Ranges Form

During the course of a study, your laboratory may obtain renewed certification or change equipment resulting in different normal ranges. The date of the change and the new laboratory normal range values must be provided to the sponsor or data center as instructed, and documentation of renewed certification submitted.

IRB Correspondence

In addition to the items originally submitted to the IRB, all additional communication with the IRB should be kept in your study file. This includes:

- *Trial Progress Reports* – Reports provided to the IRB by the investigator summarizing trial progress to date. The frequency of these reports is determined by the individual IRB, and may be based on the degree of risk involved with the study.
- *Annual IRB Renewals* – Documents submitted by the investigator to obtain continued approval to conduct the study. The regulations require each protocol to be renewed by the IRB at least annually; some IRBs request more frequent review. Submit a copy of the IRB letter documenting continued study approval to the sponsor.
- *IND Safety Reports* – Reports generated by the sponsor and sent to all site investigators when a safety issue occurs. A copy of IND Safety Reports should be forwarded to your IRB; documentation of IRB notification should be kept in your study file with a copy of the IND Safety Report.

Subject Recruitment Advertisements and Educational Materials

New advertisements and changes to previously-approved recruitment and educational materials must be approved by the IRB. Keep copies of all advertisements (such as flyers, newspaper ads, and text for radio announcements) in the study file with documentation of IRB approval. See Chapter 11 for specific information about advertisements.

Screening Log

Sponsors may require each site to complete a *Screening Log* to list all subjects who were screened for study enrollment, including those

who were screened but not enrolled. The log should be updated continually throughout the trial identifying the reasons that potential subjects are not enrolled.

Confidential Master Subject Log

A *Confidential Master Subject Log* may be provided as a mechanism for recording all subjects enrolled in the study. The log can be used to record subject contact information. This information may be used to get in touch with subjects to schedule outpatient and follow-up visits. Subjects may also need to be contacted if study safety concerns arise, or if new information that might affect a subject's willingness to continue participation becomes available.

Signed Consent Forms for All Enrolled Subjects

Keep a copy of each signed consent form for all enrolled subjects in your site study file. Depending on the type of trial and monitoring that will be performed, the sponsor may recommend that you keep signed consent forms in a central location in the study file, or that each consent form be kept with the individual subject data forms. Some institutions require the original consent form to be filed in the subject's medical record, while others recommend keeping the original in the site study file with a photocopy in the medical record. Be sure to determine your institution's policy in order to comply with local requirements. When subjects are required to sign a second consent form because of protocol changes, both consent forms should be kept in the study file.

Test Article Accountability Forms

Documentation of the shipment, receipt, and dispensing of the test article must be updated throughout the study. The sponsor usually provides accountability, dispensing, and invoicing forms. If these are not supplied, your institution's pharmacy forms may be used as long as the appropriate information is documented. Refer to Chapter 13 for additional information regarding accountability forms.

Serious and Reportable Adverse Event Forms

In each study, sponsors designate certain adverse experiences as events that must be reported in an expedited manner. Examples of

Figure 12.4 Sample Confidential Master Subject Log

HEAT
Hypothetical Example of A Trial

Confidential Master Subject Log

Investigator Name: _____ Site #: _ _ _ Page __ of __

ICH Guidelines require keeping a master subject identification log to serve as proof that the site's subjects are real people. This list is confidential and will not be forwarded to the coordinating center at any time.

- Complete all fields for each subject randomized.
- Subject ID Number: Record a unique identifier for each subject. Appropriate numbers may include a medical record number, social security number, or driver's license number (including the state of issue).

Date Consent Signed	Subject Study Number	Subject Initials	Subject ID Number (Medical Record, SS, Driver's License)	Subject Phone Number
	_ _ _ - _ _ _ _ (site# / subject#)	____ ____ ____		
	_ _ _ - _ _ _ _ (site# / subject#)	____ ____ ____		
	_ _ _ - _ _ _ _ (site# / subject#)	____ ____ ____		
	_ _ _ - _ _ _ _ (site# / subject#)	____ ____ ____		
	_ _ _ - _ _ _ _ (site# / subject#)	____ ____ ____		

such events include death, stroke, thrombocytopenia, and anaphylactic shock; however, the specific events requiring expedited reporting will vary based on trial design and phase. Reporting forms should be completed and submitted to the sponsor within 24 hours of the investigator learning of the event. This early reporting system allows the sponsor to obtain information in a timely manner consistent with the regulatory requirements, rather than at a much later date, when data forms are submitted.

Keep copies of all completed serious and expedited AE reports submitted to the sponsor in your study file. Follow-up AE information that is reported to the sponsor should be filed, as well as documentation of IRB notification and acknowledgement. Chapter 6 contains additional information about AEs and reporting requirements.

Subject Data Forms and Query Forms

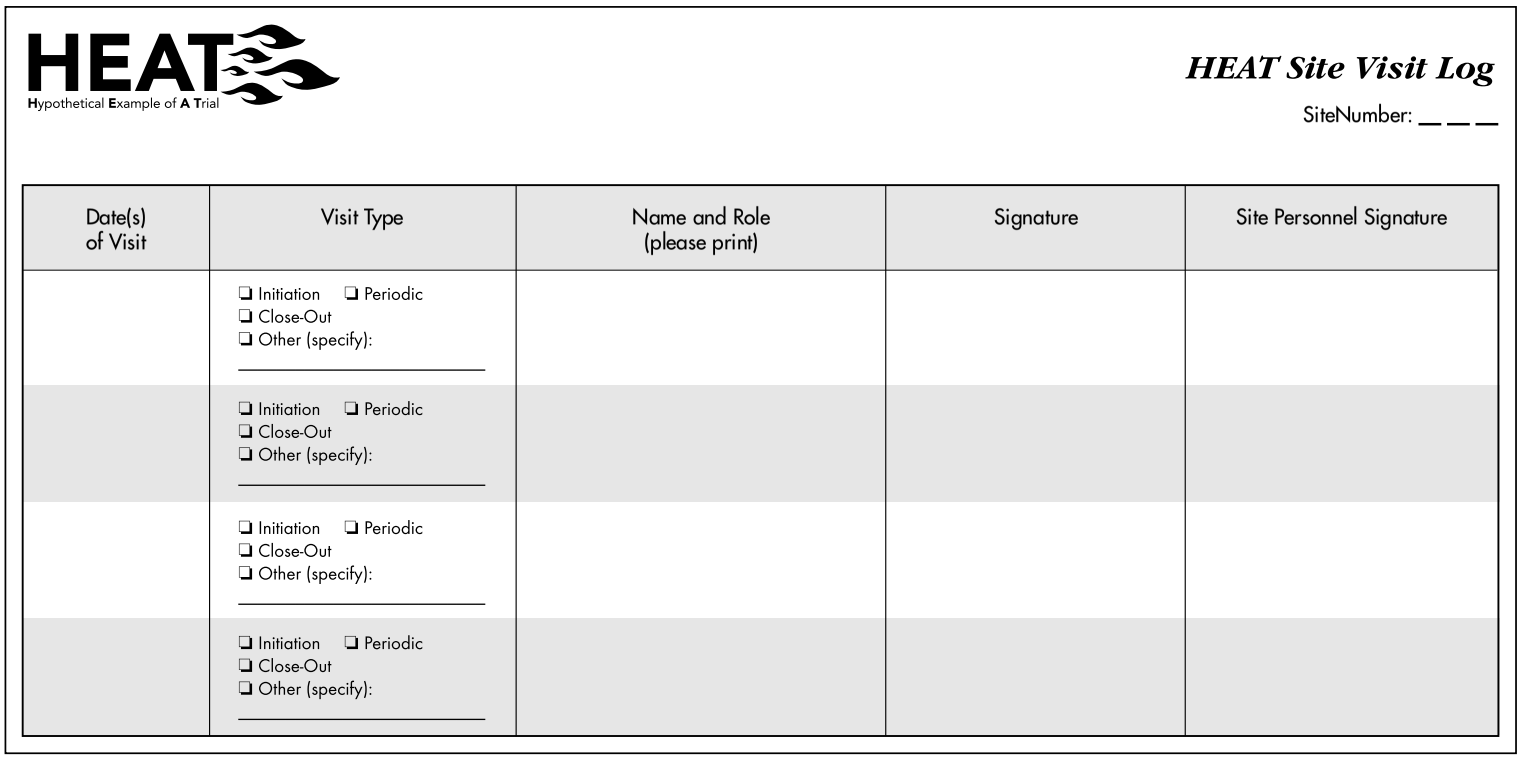
Throughout the study, subject data forms must be completed and submitted to the sponsor, CRA, or data center. Copies of all initial data forms and subsequent changes to the data must be kept at the site. Changes to the data after the data forms have been submitted may be initiated by the CRA, CRC, or by sponsor data management personnel whenever incorrect data, missing data, or data outside the expected range of responses are identified. Records of these changes must be kept as part of the study file. When recording data electronically, instructions will be provided regarding the correct method to store and back up data records.

Questions concerning data may be reported on a data query form or generated electronically. When the data center sends queries regarding data, the CRC must review the data in question, and either confirm the original data or provide corrected information. Specific instructions for returning the query responses to the data center will be provided. You should also be provided with instructions on how to correct data errors that you identify after the initial submission of data. Carefully follow the instructions provided, so that the data records at your site match those at the sponsor and data center.

Source Documents

You do not need to keep copies of source documents in your study file unless you have reason to believe that the source documents needed for verification of subject data during monitoring visits, audits, or inspections may be difficult to retrieve. If you have created forms to capture source data, you will want to keep these completed

Figure 12.5 Sample Site Visit Log



HEAT
Hypothetical Example of A Trial

HEAT Site Visit Log

SiteNumber: _ _ _

Date(s) of Visit	Visit Type	Name and Role (please print)	Signature	Site Personnel Signature
	❑ Initiation ❑ Periodic ❑ Close-Out ❑ Other (specify): _____			
	❑ Initiation ❑ Periodic ❑ Close-Out ❑ Other (specify): _____			
	❑ Initiation ❑ Periodic ❑ Close-Out ❑ Other (specify): _____			
	❑ Initiation ❑ Periodic ❑ Close-Out ❑ Other (specify): _____			

source documents in your study file with each specific subject's data forms. For these forms to be considered source documents, they must be signed and dated by the person recording the data.

Signature and Delegation Log

The *Signature and Delegation Log* is a form used to record the signature and initials of all individuals who record data on the subject data forms or query forms during the trial. Signature and Delegation Logs are also used to document staff authorization to perform study procedures and activities as delegated by the PI.

Site Visit Log

Monitors (or CRAs), who perform on-site visits and oversee the progress of the trial at the site, sign the *Site Visit Log* when conducting on-site visits (see Chapter 7). The log typically provides a place to document the date and type of visit and the name of the person conducting the visit. When a sponsor representative performs an audit, or if an FDA official arrives for a site inspection, the Site Visit Log must also be signed by these persons.

Written Communication and Correspondence

All study communication and correspondence between the PI, CRC, sponsor, laboratories, pharmacy, and others involved in the trial should be kept in the study file. This includes e-mail communications, study newsletters, and faxes sent as updates during the course of the trial. Minutes of your study team meetings should be written and filed. Include all reports from monitoring visits and other communication with the sponsor. Written documentation of telephone conversations, including discussions with "helpline" personnel, CRAs, the sponsor, and the data center, should be kept and filed.

Source Documents

Data recorded in subject data forms and case report forms may be reviewed by the monitor and compared to the data recorded in *source documents*, which are the documents or records where data is first recorded.

ICH E6 guideline for Good Clinical Practice provides the following definition of source documents in item 1.52:

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

Documents at Study Close-out

A number of documents will be required at the end of the study. Depending on the trial, the CRA may collect documents at the final on-site monitoring visit, or you may be asked to submit final documents to the sponsor by postal mail, electronically or via e-mail, fax, or courier.

Drugs and Biologics – *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. [21 CFR 312.62(b)]

Devices – *Case histories*. A participating investigator must maintain accurate, complete, and current records of each subject's case history and exposure to the device. 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. [21 CFR 812.140(a)(3)]

Outstanding Data Forms and Query Forms

Data inconsistencies or errors can be identified long after the study is completed. These issues must be resolved so that accurate and complete data are submitted with the marketing application to the FDA. All data queries must be answered and records kept in the study file to provide an audit trail.

Complete Sets of All Subject Data Forms

At the end of the study, you will need to keep a complete set of signed and dated data forms for each subject. The case report form, follow-up forms, serious adverse event forms, query forms and all other data forms relevant to each subject should be kept together in your file. In trials with electronic data records, a CD or DVD with site-specific subject data will be sent to sites after the database is locked. This should become part of the study file and must be available for audits and inspections that occur after study completion and closure.

Final Reports

The IRB and the sponsor both require a final study report from the PI. The format and specific content of the IRB final report is usually provided by the IRB, but generally includes the date the study is completed, the number of subjects enrolled, and the types and severity of any adverse events including serious, unexpected, or life-threatening events. The report should include a comment that all subjects have completed study-related treatment or have completed participation in the study. A sample Final Report is shown on the opposite page.

The sponsor may accept a copy of the report to the IRB as the final report, or may require a format that differs from that of your IRB. Regulations require that the final report be submitted in a "timely manner" for investigational drug trials, and within 3 months of study completion for device trials.

Test Article Accountability Records

The sponsor determines if unused or damaged study drug or biologics should be shipped to a designated location at the end of the study or destroyed at the site. If destroyed on-site, an institutional standard operating procedure (SOP) for the destruction of clinical test materials is needed. In device trials, unused devices are usually returned to

Figure 12.6 Sample Final Report

February 17, 2009

IRB Chairperson
Medical Center
Anytown, USA

Re: IRB # 2345-01 HEAT: Hypothetical Example of A Trial

Dear IRB Chairperson:

This letter serves as notification of the closure of enrollment and the completion of subject follow-up at our institution in the study noted above. Enrollment ended February 2, 2009, with a total of 135 subjects. The sponsor estimates that 30 day follow-up will be completed at all remaining sites by the end of March, 2009. Ten subjects were consented and enrolled in this study at our institution. Of these ten subjects, there were five Caucasian males, two Native American males, two African American males, and one African American female. None of the subjects withdrew prematurely.

During the course of this study, the Institutional Review Board was notified of two sponsor-reported serious adverse events in a letter dated November 6, 2008. In addition to these two events, one serious adverse event occurred at our institution. The IRB was notified December 1, 2008, regarding the subject RDU (#003) who developed sepsis, with blood and urine cultures positive for E. *coli*. This event was believed unlikely to be related to study medication. The subject recovered and was discharged home with no sequelae.

There was one amendment to the original protocol, dated April 08, 2008, that added a dyspnea scale to be performed 8 hours after study drug administration. IRB approval was received April 30, 2008.

There are no preliminary results from the trial at this time. No sponsor audits or FDA inspections were performed during this study. We will notify the IRB at the time of study completion nationwide, probably sometime in April, 2009.

Please contact me if you have any questions. Your signature below indicates receipt of this letter; please forward a copy to me for our study files. Thank you for your attention to these matters.

_____ _____

Principal Investigator Chair, Institutional Review Board

Test Article Disposition

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 21 CFR 312.59. [21 CFR 312.62]

Disposing of device. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs. [21 CFR 812.110(e)]

the sponsor. Specific directions regarding where to send damaged or malfunctioning devices should be provided to sites. Appropriate accountability records must be maintained to document the management and final disposition of all test articles.

Maintaining Your Site Study File

All forms and documents listed in this chapter, plus any other study-related documents, should be included in your site study file. This file should be created at the beginning of the study and updated as the study progresses. Keep all versions of each document in the file; for example, both the original IRB-approved consent form and a revised IRB-approved consent form should be kept. Devise a method of filing that is organized and consistent; for example, if you choose to file documents in regulatory sections, you should consistently file documents in their respective section, in chronological order (i.e., by date), such as most recent on top or vice versa. This will make it easy for you to find and retrieve items in your study file, and will facilitate review for monitors, auditors, and inspectors.

Record Retention

The site study file and subject data forms must be kept for **at least 2 years following the approval** of a New Drug Application (NDA), Biologics License Application (BLA), or a Premarket Approval (PMA) application for a device. If the sponsor decides not to file an application for marketing, the storage period requirement is 2 years after the sponsor notifies the FDA that the study has been discontinued. It is important to realize that the investigational product may be in clinical trials for many years before the sponsor submits a marketing application. If you participate in a trial early in the testing phase, it may be many years before the marketing application is submitted and approved, requiring you to store study records for a long period of time. Some sponsors require even longer record retention than specified in state or federal regulations – up to 15 years for some international trials. These requirements for sites to preserve records ensure that the data are available for review by the sponsor, FDA, and other regulatory authorities if needed. Check with the study sponsor to be sure you are storing study records for the appropriate period of time and do not discard or destroy records without first communicating with the sponsor.

If the PI relocates after study procedures and follow-up have been completed, the study file and trial records may be transferred to another individual at the institution who is willing to accept responsibility for maintaining the records for the required time period. The sponsor must be notified in writing of the name and address of the individual assuming responsibility. If no one at the site is willing or able to accept responsibility for the documents, the PI must take the documents to his or her new location or institution and notify the sponsor of the new address. If this is not an option, the PI will need to discuss other alternatives for record retention with the sponsor.

Principal Investigator Status Change

If the PI leaves the institution during the study and identifies a replacement PI, both the study sponsor and the IRB must be notified. A new Form FDA 1572 or Investigator Agreement identifying the new investigator must be signed by the new PI and submitted to the sponsor for approval; the full IRB committee must also review and approve the change of investigator. If a replacement PI cannot be identified, the sponsor must be notified and the study discontinued at the site. The sponsor will provide the PI with instructions on how to close out the study; a Final Report will need to be submitted to the sponsor and to the IRB.

Final Financial Disclosure Report

The regulations in 21 CFR 312.64 and 21 CFR 812.110(d) require financial disclosure reports from investigators throughout the duration of the study and for 1 year following study completion. Investigators should submit financial disclosure information in the format requested by the sponsor.

Sample Study File Organization

The following is one example of how a site study file may be organized. The study file must be available for review by monitors, sponsor auditors, and FDA inspectors.

Record Retention Period for IDE Device Trials

Retention Period. An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. [21 CFR 812.140(d)]

Record Retention Period for IND Drugs and Biologics Trials

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. [21 CFR 312.62(c)]

Transfer of Record Retention Responsibility for IDE Device Trials

Records Custody. An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in paragraph (d) of this section and transfer custody of the records to any other person who will accept responsibility for them under this part, including the requirements of 812.145. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.
[21 CFR 812.140(e)]

Study File Organization

1. Protocol and amendments
   - Copy of each protocol version
   - Protocol amendments
2. Signed Form FDA 1572 (or Investigator Agreement in device trials)
   - Original and updated Form FDA 1572
3. Confidentiality Agreement/Letter of Agreement
   - Signed Confidentiality Agreement/Protocol Signature Page
4. Site Personnel
   - CV/résumé or Statement of Qualifications for PI, co-PI, sub-investigators, and any other study personnel listed on the Form FDA 1572
   - Medical licensure forms/copy of DEA license when applicable
   - Financial disclosure information
   - Certificates of meeting attendance and training records
5. Investigator's Brochure (all versions)
6. Institutional Review Board (IRB)
   - Dated IRB membership information and/or written assurance number
   - Initial submission letter and protocol documents requesting approval
   - IRB letter stating approval of protocol and consent form
   - Letters and revised documents (protocol amendments and revised consent forms) submitted for approval
   - IRB letter(s) stating approval of protocol amendments and revised consent forms
   - IRB letter(s) stating approval of advertisements and all subject materials (may be included in a single letter stating approval for protocol, consent form, advertisements, and subject materials)
   - IND Safety Reports, documentation of submission to IRB, and IRB response
   - Reports to IRB about progress of study (at IRB specified timepoints)
   - Final reports to IRB and sponsor
7. Consent Form
   - Blank copy of all approved versions of the consent form
   - Copies of signed consent forms for all enrolled subjects (or a note stating the location where signed subject consent forms are stored)
8. Copies of IRB-approved advertisements and subject materials
9. Screening Log
10. Confidential Master Subject Log (listing all enrolled subjects)
11. Laboratory Certification and Laboratory Normal Ranges Form
12. Test article accountability
    - Packing Invoice/Receipt of test article records
    - Inventory log
    - Dispensing log
    - Records of disposition and/or return of unused or damaged test articles

13 Blank copy of the case report form and instructions
14 Serious Adverse Events (SAE) Report Forms
- Blank copy of SAE Report Form
- Copies of all completed SAE Report Forms for enrolled subjects (or note stating the location where all completed SAE reports are stored)

15 Signature and Delegation Log (indicating delegation of study activities and the individuals completing data records)
16 Site Visit Log
17 General correspondence
- Letters
- Memorandums
- Written documentation of telephone conversations
- Faxes
- Electronic (e-mail) communication between the site and the monitor, sponsor, and other trial-related groups
- Newsletters

References

1 21 CFR 312.30
2 21 CFR 56.110

13 Management of Study Drugs, Biologics, and Devices

In this Chapter

- Storing your supply of test products
- Maintaining accountability records
- When and how to unblind treatment
- What to do with unused test products when the trial is over

"*A corrected Anti-Epileptic Water of Languis*. Take shavings of man's scull, mistletoe of the oak, roots of piony, and white dittany, of each two ounces; fresh flowers of lilly convally, two handfuls; of lavender, rosemary, and tilet, of each three handfuls; cinnamon, six drams; nutmeg, half an ounce; cloves, mace, and cubebs, of each two drams; being all bruised, put them into a matras close stopp'd, in eight pints of malmsey; let them macerate for a week over a very gentle fire; then distill them on a moderate sand-bath, and keep the water for use."

Moses Charras (1619–1698), from *Royal Pharmacopoeia*, translated in English (London 1678)

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

During the start-up phase of a clinical trial, you should develop a plan for managing the product under investigation in the study. The protocol should provide clear and detailed information regarding the receipt, storage, dispensing, and return of study supplies. Your plan for the management of the test product should:

1 identify site personnel who will receive the test product;
2 outline requirements for handling the test product;
3 specify the location where the test product will be stored;
4 determine whether there are special storage needs, such as refrigeration; and
5 identify how unused test products will be returned during and at the conclusion of the trial.

Factors such as the trial randomization method, the design and packaging of test products, and the location of subjects at the time test products will be used or administered will influence the development of the plan.

The U.S. Food and Drug Administration (FDA) strictly mandates the labeling, packaging, shipping, and accountability of investigational products. The sponsor must assume these responsibilities for device trials, but in trials of drugs or biologics may delegate them to an independent agency or study pharmacy that has experience in managing investigational drugs.

Study Drugs and Biologics

In this section, references made regarding study drug also apply to study biologics.

Study Drug Accountability

The meticulous record-keeping required to track the shipment, receipt, dispensing, and final disposition of investigational products in clinical trials is commonly called "study drug accountability" and is a necessary part of ensuring that investigational products are administered to the appropriate subjects at the assigned doses and schedules. The sponsor or study pharmacy usually supplies specific forms to aid in tracking study drug accountability, but as an investigator, it is ultimately your responsibility to ensure that documentation is completed accurately and on time.

Study Drug Packaging

Study drug may be prepared and packaged in a variety of ways; in a blinded study, these preparations and packaging are designed to help maintain the study blind. Oral study drug may be supplied in blister packs, bottles, or cartons while intravenous medications may be supplied in ready-to-administer vials, or in bottles with a separate vial of diluent for mixing before administration. When multiple items such as special filters or syringes are needed to prepare and administer study drug, they may be packaged with the study drug in a box or kit. A unique identifying number is generally located on the outside of the box, bottle, or vial, and the study drug box may be sealed so that it cannot be opened until assigned to a subject. The package should be labeled with the statement "Caution: New Drug – Limited by Federal (or United States) law to investigational use." In trials with blinded study drug, both active drug and placebo will be given identical packaging and labeling to prevent accidental breaking of the blind.

Figure 13.1 Study Drug Packaging

Study Drug Receipt

Study drug usually arrives at the site accompanied by a *Packing Invoice*. When study drug supplies arrive, personnel receiving the study drug must record the date of arrival and verify that the contents of the shipment match those listed on the Packing Invoice. The contents must be examined for any broken or damaged supplies, and any expiration dates must be checked. The shipment will include instructions on how to acknowledge receipt of study drug, and what should be done if there is an error on the Packing Invoice or if materials are damaged. Personnel who are responsible for receiving study drug and verifying the contents should follow up on any discrepancies or concerns immediately. Keep copies of all Packing Invoices and receipt acknowledgments in your site study file.

Study Drug Storage

Instructions regarding the storage of study drug and special requirements, such as refrigeration at a specified temperature, will be included with the shipment, in the protocol, or in a study drug reference manual. All study drug supplies must be stored in a secure location with limited access to avoid use or tampering by unauthorized personnel.

Depending on the trial, study drug may be stored in various locations at the site. For example, when subjects are administered study drug in an outpatient setting, study drug should be stored in a location convenient to where the visits will be conducted. If subjects are administered study drug in the emergency department, it may be beneficial to store study drug in a secure location nearby. If a study is blinded or if specific kit numbers are assigned at randomization, it is important that you never split the inventory between locations (e.g., two outpatient clinics). Each location should be considered a separate site with its own supply of study drug.

Handling 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. [21 CFR 312.69]

Dispensing Study Drug

To ensure that only enrolled subjects receive study drug, you will need a reliable system for dispensing study medication. This system should take into account the individuals who will be responsible for dispensing study medication, the Clinical Research Coordinator (CRC) or pharmacist, and the circumstances surrounding the initiation of study drug (e.g., taking place in an acute setting such as the emergency department, or in a planned situation such as an outpatient

Figure 13.2 Sample Packing Invoice

XYZ PHARMACY

HEAT
Hypothetical Example of A Trial

PACKING INVOICE

Site Address: _____

Pharmacy Contact: _____

Principal Investigator: _____

Shipped On: _____

BULK DRUG

Lot Number	Description	Quantity
	Total items shipped	____ vials

Please compare shipment contents to Packing Invoice. If discrepancies or damaged items are found, note them below and immediately notify the XYZ Pharmacy by phone. Sign and date copies provided, return one copy to the XYZ Pharmacy and retain the other copy for your records.

Received by: _____ **Date:** _____

Problems noted: _____

XYZ Pharmacy
1234 Technology Drive
Durham, NC 27704, USA
Phone: (919) 123-4567, Fax: (919) 123-3333

SITE COPY

Figure 13.3 Sample Drug Accountability Form

HEAT
Hypothetical Example of A Trial

HEAT Study Drug Accountability Log

Site Number __ __ __

Principal Investigator: ____________________________
Pharmacy Contact: ____________________________

Kit Number	Assigned to		Date	# of Kits Rec'd	Dispensed by Initials	Status* (use code below)	# of Vials Used/ Date Returned		Date Kit Destroyed	Initials	Witness Initials	CRA Initials/Date
	Subject Number	Subject Initials										
							Initial Stock					
_ _ _ _ _ _	_ _ _ - _ _ _	_ _ _					❑ 1 ❑ 2					
_ _ _ _ _ _	_ _ _ - _ _ _	_ _ _					❑ 1 ❑ 2					
_ _ _ _ _ _	_ _ _ - _ _ _	_ _ _					❑ 1 ❑ 2					
_ _ _ _ _ _	_ _ _ - _ _ _	_ _ _					❑ 1 ❑ 2					
_ _ _ _ _ _	_ _ _ - _ _ _	_ _ _					❑ 1 ❑ 2					
_ _ _ _ _ _	_ _ _ - _ _ _	_ _ _					❑ 1 ❑ 2					

* Status codes:
1 Subject randomized and received any amount of study drug
2 Kit opened but subject did not receive any study drug
3 Kit assigned but not opened
4 Kit damaged and not used

Signature log for personnel completing this form:

Date	Printed Name	Signature	Initials	Date	Printed Name	Signature	Initials

Principal Investigator (PI) signature and date:
PI to sign at the end of the study

Date: ____/____/____

clinic or medical office). The system should also accommodate the need to verify subject eligibility for the study and, when applicable, to notify the study pharmacist when starting and stopping study drug. Every study drug kit, bottle, or vial must be accounted for to ensure that only subjects participating in the study receive the investigational treatment. The sponsor or designated study pharmacy usually supplies drug accountability forms that should be updated every time study drug is dispensed to the subject or returned.

There are occasions where commercially available drug is supplied as part of a clinical trial. It is important to segregate this material from regular hospital inventory to ensure that it is only given to subjects enrolled in the clinical trial. Best practice would be to label this material specifically for the protocol, although this is not always done.

In an outpatient trial, subjects may be given one or more bottles of medication to take over a specified period. When dispensed, each bottle or blister pack of study drug should be clearly labeled with the subject study number and initials. Subjects should be instructed to bring their study medication to each follow-up visit so that remaining pills can be counted and returned if necessary. In these trials, accountability forms require documentation of study drug use with both a dispensing date and a return date. In a trial where an intravenous agent is administered, study medication is usually recorded with only a dispensing date and no return date. The accountability forms should be designed to capture information appropriate to the specific design of the study and the study agent involved.

Study agent administration should be documented in the subject's medical record or chart as well as on the study accountability records. It is critical to carefully record study medication use as it occurs, and to sign or initial all entries on the accountability forms and in the medical record.

Study Drug Unblinding

There are very few appropriate reasons for breaking the study blind, but they include situations in which the course of a subject's treatment depends on knowledge of which study agent was administered.

While unblinding is a rare event, information about when and how unblinding may occur should be provided to all investigators. Methods of unblinding include tear-off labels, a telephone call to a central call center or the medical monitor at the sponsor, and sealed envelopes containing the study treatment assignment or dose. Whichever method is used, remember that unblinding is appropriate

Control of Investigational Agents

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. [21 CFR 312.61]

Should You Unblind?

A subject receives an investigational drug with the potential to cause bleeding, and there is no drug known to reverse its effects. In this case, serious bleeding events should be treated by stopping ongoing study drug administration. Unblinding study treatment is not appropriate in this example, because knowing the specific agent or the dose administered would not change the treatment plan, which might include blood transfusions, pressure to the area of bleeding, and other supportive measures.

only in a very few situations and site personnel should consider carefully before doing so.

Final Disposition of Study Drug

The sponsor will decide whether study drug or other study articles should be returned by shipping to a designated location or destroyed at the site. Depending on the trial design, study drug may need to be returned during a trial (for example, if unused study drug has expired) or at study completion. When study drug supplies are returned to the sponsor or designated study pharmacy, site personnel should document the date, the name of the person to whom the supplies were sent, identifying information such as box or bottle numbers, and the quantity sent.

If the sponsor authorizes you to destroy study drug at the site, record the date, quantity, means of destruction, and name of the person who destroyed study drug. The final disposition of all study drug supplies should be documented on the appropriate study accountability forms.

Study Devices

Device accountability has many of the same requirements that apply to studies of drugs and biologics. Records regarding the shipment, receipt, use of device, and final disposition of devices must be maintained as part of the site study file.

In addition, there are a few aspects unique to clinical trials of devices, including specific labeling requirements, accountability, and tracking.

Device Labeling

Under 21 CFR 812.5, an investigational device or its immediate package must bear a label with:

- the name and place of business of the manufacturer, packer, or distributor;
- the quantity of the contents, if appropriate; and
- the statement "CAUTION Investigational device. Limited by Federal (or United States) law to investigational use."

The label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

The sponsor should provide detailed information on device labeling in the protocol. This information will vary depending on the device and the nature of the study. Product labeling should be sufficient to ensure stability of the device for the duration of the study (e.g., storage requirements, calibration procedures), bear sufficient directions for proper administration or use, and detailed procedures to follow in the event of device malfunction or subject injury.

Device Accountability

The accountability records for devices shipped to investigative sites should include the batch number or code number of the device(s) as well as the name and address of the investigative site. Accountability records (and/or subject data records) may also require documentation of each subject's exposure (period of use) to the device.

Device Tracking

Devices require long-term tracking to assess safety after they are approved for marketing. Each device is assigned a unique number. In clinical trials, investigator records must indicate units that were returned to the sponsor, repaired, or otherwise disposed of.

Health care providers should report post-marketing adverse events and device problems to the device manufacturer or to the FDA using MedWatch Form FDA 3500. Used for voluntary reporting, Form FDA 3500 may be submitted online at (www.fda.gov/medwatch/report.htm), or by mail, telephone, or fax.

Mandatory reporting of adverse events and device problems are required of user facilities (hospitals and nursing homes). Currently Form FDA 3500A cannot be submitted online; paper copies must be completed and submitted to the Center for Devices and Radiologic Health (CDRH) at the FDA.

14 Managing Clinical Trial Data

In this Chapter

Clinical Trial Data and:

- HIPAA and the Privacy Rule
- Applicable regulations
- Study site responsibilities
- Source documents
- Confidentiality

"Science is organized knowledge."

Herbert Spencer (1820–1903), British Philosopher

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

Clinical trials are designed to answer questions regarding treatment(s) identified in the research protocol. To arrive at the answers to these questions, data from research subjects are collected, recorded, and submitted to the sponsor or a designated data center.

Individually identifiable health information is information that is a subset of health information, including demographic information collected from an individual, and:

1 is created or received by a health care provider, health plan, employer, or health care clearinghouse; and

2 relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and

   i) that identifies the individual; or

   ii) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.[2]

HIPAA, the Privacy Rule, and Clinical Trial Data

Ever since the *Health Insurance Portability and Accountability Act (HIPAA)* was enacted in 1996, it has had an impact on the collection, storage, transmission, and disclosure of research data. As discussed in Chapter 3, HIPAA was initially enacted to allow employees to maintain health care insurance after leaving a job. Congress added an administrative simplification section to the bill to reduce costs by simplifying and standardizing health care transactions through electronic filing of insurance claims and other reimbursement-related documents. Subsequently, however, concern about the privacy and security of this electronically transmitted health care data led the Department of Health and Human Services (DHHS) to develop rules defining and protecting an individual's health information. The resulting *Privacy Rule*, implemented in 2003, established a set of national standards that protect individually identifiable health information, known as *protected health information* (PHI). According to DHHS, "Health care providers have a strong tradition of safeguarding private health information. However, in today's world, the old system of paper records in locked filing cabinets is not enough. With information broadly held and transmitted electronically, the Rule provides clear standards for the protection of personal health information."[1] Because clinical researchers are also functioning as health care providers as they provide clinical care to research subjects, the Privacy Rule applies to the collection and transmission of the health information data in a clinical trial.

Several aspects of the Privacy Rule apply to the collection, storage, and transfer of clinical trial data. In the context of research, the Privacy Rule protects the privacy of individually identifiable health information while also ensuring that researchers have access to necessary medical information for research purposes. Researchers are allowed to use or disclose health information from which elements capable of being used to identify a specific person have been removed ("de-identified").[3]

The Privacy Rule allows researchers to use and disclose individual protected health information with individual authorization (permission), or in specific situations, without individual authorization.

Use of Protected Health Information With Individual Authorization

The Privacy Rule allows researchers to use or disclose PHI for research purposes when the study subject has given authorization. For most clinical trials a research subject's authorization is requested. The request for authorization is often included in the consent form for the clinical trial but may also be requested in a separate consent document.

Research authorization may state that the authorization does not expire. A statement that there is no expiration date or that the authorization continues until the "end of the study" is acceptable.

Use of Protected Health Information Without Individual Authorization

The Privacy Rule contains a broad exception to the requirement for authorization. This exception provides for a waiver of authorization allowing the use of PHI data in certain situations. Researchers can request institutional review board (IRB) or privacy board approval to waive the requirement for authorization; for example, when conducting records research or when doing preliminary work to develop a protocol. Three criteria must be satisfied in order to waive individual subject authorization:

1 The use or disclosure of PHI involves no more than a minimal risk to an individual's privacy based on the presence of the following elements:
   a) there is an adequate plan to protect the subject identifiers from improper use and disclosure;
   b) there is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law, and
   c) there are adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use of disclosure of protected health information would be permitted by this subpart.[4]
2 The research could not be done without the waiver of individual authorization.
3 The research could not be done without access to and the use of the PHI.[5]

Researchers can also obtain a waiver of authorization in situations where the PHI is used solely to design or prepare a research protocol. A waiver of authorization may also be obtained when research is being conducted on persons who have died and the information is necessary for the research being conducted; researchers must be prepared to show documentation of deaths, if requested.

Subjects can revoke authorization of researchers' use of their PHI but are required to do so in writing. Investigators are not allowed to make treatment or benefits contingent upon a subject authorizing use of his or her PHI.

Subject Identifiers

Examples of subject identifiers include but are not limited to:

1. Name
2. Mailing address
3. E-mail address
4. Telephone and fax numbers
5. Social security or other national identification numbers
6. Medical record/case note numbers
7. Vehicle license plate numbers
8. Biometric identifiers, such as fingerprints
9. Images that allow the identification of a subject

Subject Identifiers

Subject identifiers are elements that can directly identify an individual. To protect private health information, researchers *de-identify* the data, meaning that they separate the data from any identifying information that can link the data to the specific individual. Subject identifiers should not be recorded on data forms, in the database, on coding forms, or any other study documents. Subject names should be recorded and kept in a separate location, to be available when source document verification or subject follow-up is required. Study subjects should be given a unique study number that serves as their identifier. The unique study number is usually associated with subject initials and is used on all study documents throughout the clinical trial.

Guidelines and Regulations Regarding Clinical Trial Data

Relevant guidelines regarding clinical trial data can be found in the International Conference on Harmonisation (ICH) E6 guidelines for Good Clinical Practice (GCP). As provided in Section 1.24, the definition includes the statement that GCP "provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected."

ICH E6 Section 2: The Principles of ICH GCP

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

ICH E6 Section 4: Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the [case report forms] CRFs and in all required reports.

4.9.2 Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators' representatives on making such corrections.

21 CFR 312 and §812

Regulatory requirements regarding investigator responsibilities for clinical trial data can be found in the U.S. Code of Federal Regulations (CFR) in 21 CFR 312 (for drugs) and 21 CFR 812 (for devices).

21 CFR 312.62(b) 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 investigations.

21 CFR 812.140(a)(3)(ii) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

Electronic Data

While the ICH E6 guidelines regarding clinical trial data apply to both paper and electronic data, the CFR contains regulations specific to

electronic records. These can be found in 21 CFR 11 – *Electronic Records* and *Electronic Signatures*. These regulations establish the criteria under which the U.S. Food and Drug Administration (FDA) will accept electronic records and signatures as trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper. The following list summarizes some of the requirements outlined in the regulations.

1 The software used for the system must be validated. That is, its accuracy, reliability, and ability to detect invalid or altered records must have been tested and established.

2 It must be possible to generate accurate, legible copies of the electronic records, suitable for the FDA to inspect, copy, and review.

3 The records must be protected throughout the required retention period, available for accurate and ready retrieval, even if the software that created those records is no longer in use.

4 Access to the system that contains those records must be reliably limited to authorized individuals only.

5 Personnel who develop, maintain, and use these records must have documented education, training, and experience appropriate for their roles.

6 Every electronic record must have a secure, computer-generated date- and time-stamped audit trail, maintained for as long as the underlying e-record, and also be available to the FDA for review and copying. Record changes must not obscure previously recorded data.

7 Reliable change control procedures, with their own time-sequenced audit trails, must be in place.

8 Written policies must exist, establishing that the record producer recognizes that anyone using an electronic signature is responsible and accountable, just as would be the case for a handwritten signature. Accompanying the signature in clear text must be the printed name of the signer, the date and time when the signature was executed, and the meaning of the signature (e.g., review, approval, responsibility, authorship). The system must prevent the signature from being removed, copied, or repudiated by the signer.

9 Strict requirements for passwords and other security measures must be implemented to prevent access to and falsification of e-records.

The Origin of 21 CFR 11

In the early 1990s, the Burroughs-Wellcome Company, a pharmaceutical company then headquartered in Research Triangle Park, North Carolina, was building a new sterile product manufacturing facility. To fully exploit the possibilities of this state-of-the-art facility, they wanted to be able to sign off on batch records electronically, so they petitioned the FDA to allow this approach. After careful consideration of this request, the FDA published a *Notice of Proposed Rulemaking* in 1992. Following a long period of public comment and revisions, the final rule was issued in August 1997.

Study Site Responsibilities Regarding Clinical Trial Data

From the time that data are generated until the time of data analysis, everyone who handles the data must follow certain steps to ensure the accuracy and credibility of the data, leaving an "audit trail" that indicates how data moved from one location to another, how and when any changes were made and by whom, all the while maintaining the confidentiality of subjects. It is therefore important that data are stored and handled appropriately, following regulations and GCP guidelines, so that the credibility and accuracy of the data will not be questioned.

To fulfill regulatory requirements, the principal investigator (PI) and clinical research coordinator (CRC) have many activities to complete when handling clinical trial data. These include: 1) recording the data in source documents, 2) completing data forms, 3) correcting the data, 4) submitting the data, and 5) storing the data for long-term retention.

Depending on a number of factors, including the type of monitoring, the amount of monitoring for source document verification, and whether paper or electronic data forms are being used, the order of these activities may vary. For example, clinical data on paper data forms may first be collected from the investigative site by a monitor or clinical research associate (CRA) for source document verification, transferred to data processors for data entry and computerized checks, and then submitted to statisticians for analysis and reporting. When electronic data forms are used, computerized checks may occur before source document verification; monitoring may also occur after data entry and computerized checks have been completed. The data will be returned to the investigative site when data confirmation or correction is needed, or when questions about the data are generated by the statistical review.

Record the Data in Source Documents

Source documents are the original records where subject information is first recorded. Source documents are typically signed and dated by the person completing them and may include, but are not limited to:

- All components of inpatient hospital or outpatient clinic records
- Consultation reports
- Procedure and laboratory reports

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). [ICH E6: Good Clinical Practice: Consolidated Guideline 1.51]

- Pharmacy records
- Transport records, including ground and air transportation
- Source data forms created to record pertinent data
- Subject diaries
- x-rays and film reports

There are several key points regarding the recording of data in source documents:

1 *Data recorded in source documents should be thorough and complete.* The industry adage is that if something is not written down, it is assumed that it did not happen. For example, the PI performs an eye examination on a study subject; because the exam is normal the PI does not make an entry in the clinic notes or medical records. In this case, the assumption made (for trial purposes) would be that no eye exam was done because no note was recorded. An example of what the PI should write is "Slit-Lamp Examination – No Abnormalities Detected (NAD)," or "Fundus Examination-NAD."

2 *Data recorded in source documents should be accurate and consistent.* For example, when describing a symptom experienced by the subject, the same terminology should be used throughout all data forms. Do not record the symptom as "eye pain" at one visit and "ache in eye" at a subsequent visit.

3 *Entries written in source documents should be made at the time of observation or treatment.* For example, the eye examination should be recorded on the day that it was performed. An entry made in the medical record 2 days later may appear to be contrived.

Create Worksheets and Forms as Needed

A number of circumstances might require you to develop a worksheet or a specific form to record clinical trial data. Some worksheets are simply a tool to remind individuals of when to perform study-related activities, while other forms may be used to record original data and serve as source documents.

Reminder Worksheets

The nuances of the data questions may not be apparent until you have had the opportunity to complete the data forms for your first study subject. However, a review of required data and data forms before enrollment starts will help you identify protocol-related issues, procedures, and logistical concerns, such as:

- blood samples that are required at times different from your institution's routine;

- a physical assessment that requires an evaluation different from that routinely performed;
- measurements or specific medical history items that are not typically collected or recorded in your institution's source documents.

In such cases, you may consider creating a worksheet that prompts the collection of data outside the standard routine. Such a worksheet might include a checklist of activities to be performed; the original data will be recorded in the medical record. Please note, however, that this type of worksheet is not a source document.

Figure 14.1 Sample Reminder Worksheet

HEAT
Hypothetical Example of A Trial

Reminder Worksheet

Pre-Admission

❑ Review screening lab results (drawn within the previous 7 days) to determine eligibility.
❑ Obtain written informed consent.
❑ Complete Inclusion/Exclusion Worksheet to screen the subject.
❑ Notify pharmacist to coordinate randomization and study drug preparation.

Admission

❑ Confirm subject still meets eligibility criteria.
❑ Obtain vital signs and 12-lead ECG.
❑ Place IV for study drug administration and an 18-gauge angiocath for blood draws.
❑ Obtain baseline labs and record on Lab Collection Worksheet.
❑ Start study drug.
❑ Collect labs and complete Lab Collection Worksheet as specimens are obtained.
❑ Place specimens on ice for processing.
❑ Centrifuge within 30 minutes of collection.
❑ Aliquot specimens into chilled cryovials and freeze immediately at -70°C.

Discharge

❑ Schedule fasting follow-up lab visits at 96 hours (4 days) and 168 hours (7 days) after study drug was stopped.
❑ Provide 24-hour phone numbers for subjects to call with questions or concerns.

Follow-Up 96 hours (4 days) and 168 hours (7 days) visits

❑ Place 21-gauge butterfly with 12-inch tubing.
❑ Obtain specimens and complete Lab Collection Worksheet.
❑ Centrifuge, aliquot, and freeze as noted above.

Shipping

❑ Ship specimens on the first Monday, Tuesday, or Wednesday after collection of the subject's last specimen. Refer to the shipping section of the study manual for details.

Forms to Record Source Data

You may find it useful to create a form for the purpose of recording source data; such a form will serve as a source document for data recorded on subject CRFs. This might occur when study data are not typically documented in the medical records or case notes at your site. A form can serve as the source document if the person completing it records their signature and the date. When developing this form, you will find it helpful to review the schedule of assessments included in the protocol. The schedule will indicate when procedures, tests, and other study-related activities are required; the corresponding page of the CRF will provide the specific information that needs to be recorded in the source documents.

When data are routinely recorded in the medical records, however, it is not recommended that you develop a separate form for this purpose. This creates additional work by requiring the CRC to record the source data in both the medical record and on the form, and increases the likelihood of transcription errors.

Complete Data Forms

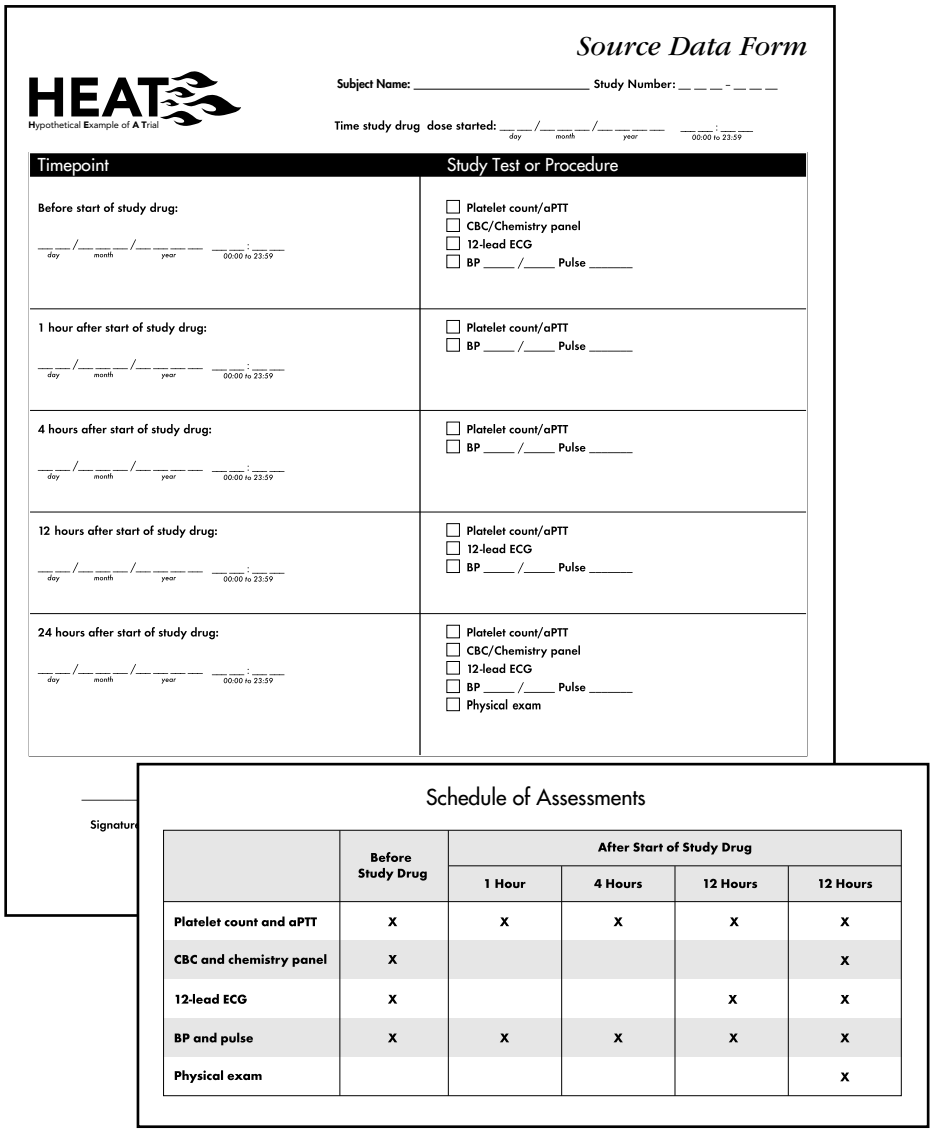
Once a subject has been enrolled and study procedures have been performed, you will need to complete the data forms. Many are designed using multiple-choice responses, with as few lines or spaces for "open" or "free" text as possible. Such a design results in data being collected using the same terminology, and allows data to be combined more easily with data from other subjects and other trials.

Free Text

When free text is recorded, all terms must be consistently recorded according to the instructions. Check with the sponsor for instructions on the following situations:

- When recording free text for an adverse event, should you record the event as a diagnosis or as symptoms? Most sponsors ask that a diagnosis be recorded instead of symptoms; for example, "congestive heart failure" rather than "shortness of breath and ankle edema."
- Although terms may be used interchangeably in clinical practice, they must be recorded consistently on data forms. For example, is "chest pain" or "angina" the preferred term; should "back ache" or "back pain" be used?

Figure 14.2 Sample Schedule of Assessments and Source Data Form



Source Data Form

HEAT
Hypothetical Example of A Trial

Subject Name: _____ Study Number: __ __ __ - __ __ __

Time study drug dose started: __ __ / __ __ __ / __ __ __ __ __ __ : __ __
day / month / year / 00:00 to 23:59

Timepoint	Study Test or Procedure
Before start of study drug: __ __ / __ __ __ / __ __ __ __ __ __ : __ __ day / month / year / 00:00 to 23:59	☐ Platelet count/aPTT ☐ CBC/Chemistry panel ☐ 12-lead ECG ☐ BP _____ /_____ Pulse _____
1 hour after start of study drug: __ __ / __ __ __ / __ __ __ __ __ __ : __ __ day / month / year / 00:00 to 23:59	☐ Platelet count/aPTT ☐ BP _____ /_____ Pulse _____
4 hours after start of study drug: __ __ / __ __ __ / __ __ __ __ __ __ : __ __ day / month / year / 00:00 to 23:59	☐ Platelet count/aPTT ☐ BP _____ /_____ Pulse _____
12 hours after start of study drug: __ __ / __ __ __ / __ __ __ __ __ __ : __ __ day / month / year / 00:00 to 23:59	☐ Platelet count/aPTT ☐ 12-lead ECG ☐ BP _____ /_____ Pulse _____
24 hours after start of study drug: __ __ / __ __ __ / __ __ __ __ __ __ : __ __ day / month / year / 00:00 to 23:59	☐ Platelet count/aPTT ☐ CBC/Chemistry panel ☐ 12-lead ECG ☐ BP _____ /_____ Pulse _____ ☐ Physical exam

Signatur

Schedule of Assessments

	Before Study Drug	After Start of Study Drug			
		1 Hour	4 Hours	12 Hours	12 Hours
Platelet count and aPTT	X	X	X	X	X
CBC and chemistry panel	X				X
12-lead ECG	X			X	X
BP and pulse	X	X	X	X	X
Physical exam					X

- When you need to record medications in a free-text format instead of using check boxes, ask the sponsor whether the medications should be recorded as a generic name or a trade name. For example, should you record "Lasix" or "furosemide"?
- How do you record combination medications? For example, do you record Dyazide, a combination medication, or should you record triamterene and hydrochlorothiazide, the names of the two combined medications?

Figure 14.3 Sample Data Form with Check Boxes and Free Text

Subject Study Number: 1 2 3 – 4 5 6 [site no.] Subject Initials: A B C (first middle last)

HEAT
Hypothetical Example of A Trial

Baseline Visit

Instructions for completing this form are on the back.

Clinical History

Does the subject have a history of any of the following?

Peripheral vascular disease:	☐ No	☒ Yes	
Cerebral vascular disease:	☒ No	☐ Yes	
Hypertension:	☐ No	☒ Yes	
Diabetes:	☒ No	☐ Yes	
Severe chronic obstructive pulmonary disease:	☒ No	☐ Yes	
Myocardial infarction:	☐ No	☒ Yes → If Yes, date of most recent:	03 (DAY) / SEP (MONTH) / 2007 (YEAR)
Cardiomyopathy:	☒ No	☐ Yes → If Yes, identify type *(check one)*:	☐ Dilated ☐ Hypertrophic ☐ Other
Ejection fraction measured within the past six months:	☐ No	☒ Yes → If Yes, what is the subject's most recent EF?	65 %
History of percutaneous coronary intervention:	☒ No	☐ Yes	
History of CABG:	☒ No	☐ Yes	
History of valvular surgery:	☒ No	☐ Yes → If Yes, check one:	☐ Mitral ☐ Aortic

Implantation Data

Date of implantation: 12 (DAY) / APR (MONTH) / 2009 (YEAR)

Does the subject have a sinus mechanism, a slow ectopic atrial mechanism, or atrial standstill?
☐ No → If No, patient may be ineligible.
☒ Yes

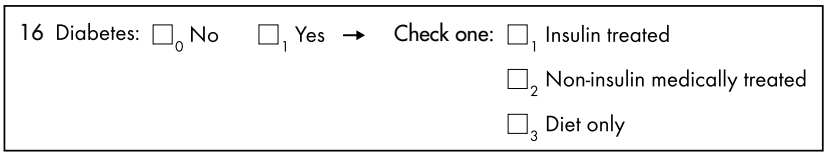
Specify the lead types that are being implanted.

ATRIAL Lead *(check one)*		VENTRICULAR Lead *(check one)*	
☒ Medtronic →	Model #: 123456	☒ Medtronic →	Model #: 654321
☐ Guidant →	Model #:	☐ Guidant →	Model #:
☐ Intermedics →	Model #:	☐ Intermedics →	Model #:
☐ St. Jude →	Model #:	☐ St. Jude →	Model #:
☐ Other →	Model #:	☐ Other →	Model #:

Conditional Data Fields

When completing all data forms, be sure to check that you have completed all required fields. Conditional data fields (known as "parent-child" fields), when checked "yes," require a response to the dependent question. For example, if you check "yes" for "diabetes," you must answer the dependent question regarding insulin use. If the response to the conditional question of "diabetes" was "no," then no response is necessary for the dependent question. In trials using

Figure 14.4 Conditional or Parent–Child Data Fields



electronic CRFs, the system will usually prompt you to complete data for conditional fields when applicable.

Also check to make sure that you have been consistent in your data responses. For example, if you indicated that a medication was discontinued in response to hypotension, then make sure you have indicated an episode of hypotension on the Adverse Event form or elsewhere in the CRF.

Data Consistency

Data must be reported accurately and consistently by all sites participating in the study. For this reason, data forms will be reviewed carefully at investigator meetings and during monitoring visits. Directions for completing the data forms are often provided so that all sites will record data consistently using the specific definitions provided in the protocol and supplemental directions.

It is important to realize that definitions of variables collected in a clinical trial may vary from those used in standard practice at your clinic or institution. For example, when you are asked to record any medical history of hypertension, it is important to know what the parameters for hypertension are. At your site, clinicians may consider a systolic blood pressure measurement of >140 mm Hg as hypertension while clinicians at other sites may consider a systolic blood pressure measurement of >130 mm Hg as hypertension. In order to ensure consistency within and across sites, these definitions must be made clear.

Consistency within a site also means that data for the trial is always taken from the most accurate and reliable source at your site. For example, a trial requires blood samples to be drawn at specified intervals following the first dose of study drug; at 30 minutes, 1 hour, and 2 hours after study drug administration. You will need to record in the CRF the time each blood sample was drawn. At your hospital, the laboratory records the time the sample is received in the lab as the time the sample was obtained from the subject, even though the actual time the sample was drawn is written on the lab requisition by the phlebotomist. Because of this known time discrepancy at your institution, you create a Source Data Form to capture the actual sample time (same time as that handwritten by the phlebotomist on the requisition), since the handwritten requisition is not included as part of the medical record. In the CRF you record the time from the

ICH Records and Reports

4.9.2 Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

Source Data Form because you know it is the most accurate and reliable source. A *letter (or note) to file* should be written to explain this situation and should be kept in your study file.

Consistency also refers to data recorded within a single CRF. For example, if you indicated in the medical history section that the subject was treated with an antihypertensive medication, this must also be indicated in the pre-enrollment medication section of the CRF. An ongoing event recorded during a follow-up visit must be recorded on the subsequent follow-up visit form, indicating whether the event is still ongoing or has been resolved.

Sometimes you will find different answers to a data question recorded in source documents. For example, in a study where a subject undergoes a cardiac catheterization to evaluate coronary artery blockage, there may be different recordings of the degree of arterial stenosis. The interventional cardiologist performing the catheterization may make a visual estimation of the stenosis at the time of the procedure, recording it as 75%. Another cardiologist or technician reviewing the angiograms after the procedure has been completed may take caliper measurements of the stenosis, measuring it as 82% and recording this in the angiogram report. Since both measurements are included in the subject's medical record, you will need to determine which is more accurate and/or consistent. In this case, because the angiogram report uses an actual caliper measurement rather than a visual estimation, you might consider it to be more accurate and decide to consistently report these data in the CRFs. A *letter to the file* should be written to explain your decision.

Data Coding

Coding is the process used to assign data to categories for analysis. Medical terms recorded on the subject data forms may need to be matched with terms in coding libraries or dictionaries to provide uniform data terminology across all subjects. Commonly used coding dictionaries include WHOART, COSTART, and MedDRA.

Dictionary	Full Name	Primary Use
MedDRA	Medical Dictionary for Regulatory Activities Terminology	Coding of Adverse Events / Medical History / Medical Terms
WHOART	World Health Organization Adverse Reaction Terminology	Coding of Adverse Events
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms	Coding of Adverse Events

Instructions should be provided to the PI and CRC regarding any specific requirements for recording data that are based on the coding dictionary used for the trial data analysis. In particular, you may be given instructions regarding the completion of adverse event free-text fields.

The following is an example of how terms recorded on subject data forms are coded and assigned to a category using the MedDRA dictionary. MedDRA has five hierarchies; from lowest to highest, they are: Lowest Level Term (LLT), Preferred Term (PT), High Level Term (HLT), High Level Group Term (HLGT), System Organ Class (SOC). Verbatim refers to the term or event recorded by the CRC on the subject data form.

Verbatim (Term recorded on CRF)	LLT	PT	HLT	HLGT	SOC
Anginal pain	Anginal pain	Angina pectoris	Ischemic coronary artery disorders	Coronary artery disorders	Cardiac disorders
Jaw pain	Jaw pain	Pain in jaw	Bone related signs and symptoms	Bone disorders (excl congenital and fractures)	Musculoskeletal and connective tissue disorders

Many cancer clinical trials use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) dictionary to define and grade the seriousness of adverse events. In this dictionary events are assigned a "short name" to simplify the documentation of adverse events in the CRF. Users must determine the applicable "grade" or severity of the event from 1 to 5, with 5 being death. Investigators can access CTCAE online where they can search the dictionary to determine the applicable event name and severity grade. Each adverse event term is ultimately mapped to a MedDRA term and code to provide consistency of terms when combining data.[6]

The following is an example of an adverse event using CTCAE:

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., keto-acidosis, hyperosmolar non-ketotic coma)	Death

Electronic record

Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.
[21 CFR 11.3(b)(6)]

Paper Data Forms versus Electronic Data Forms

Both paper and electronic data forms are currently used in clinical trials; however, over the last decade the percentage of trials using some form of *electronic data capture* (EDC) has substantially increased. There are both advantages and challenges associated with EDC, although feedback from CRCs has generally been favorable.

Advantages of EDC

The major advantages of EDC are:

Advantage: The person entering the data receives immediate feedback regarding missing or discrepant data once data are submitted.

For example: when a resting heart rate is entered as 172 beats per minute into an electronic form, a data check will ask for verification since this rate is outside an expected range programmed into the eCRF (for example, 50–120 BPM). The CRC entering the data will have the opportunity to check the source document and confirm or change the data immediately. In this example, the CRC meant to enter 72, not 172, and can immediately correct the error.

If paper forms were in use, this check would not be performed until on-site source document verification was performed by the CRA, or until the data form was submitted and the data entered at the sponsor or data center. Either method would require the CRC to request and review source documents weeks later and make corrections after the original data submission.

Advantage: Data center personnel can review the status of data entry and query resolution without waiting for paper data forms to be received in-house.

Advantage: The CRA can review the status of data entry before conducting on-site monitoring visits.

Advantage: Data are available for interim analysis; all pages of the eCRF do not need to be complete to be available for review.

Challenges of EDC

A number of challenges remain regarding the use of EDC in clinical trials; sponsors and data centers are working to provide solutions. These challenges include:

Challenge: There are multiple EDC systems in use; therefore, CRCs and other site personnel may require training on multiple systems.

Solution: Training may include written instruction manuals and hands-on training in a computer lab. As CRCs gain experience and proficiency in using EDC systems, training will become more streamlined and less time-consuming.

Challenge: Many sites do not have computers with the high-speed Internet access necessary for EDC.

Solution: Although initially difficult to obtain at many sites, high-speed Internet access has become increasingly available in medical clinics and hospitals. Sponsors may provide sites with computers and funds for Internet access, but as availability continues to increase, this is required less often.

Challenge: To perform source document verification, CRAs need high-speed Internet access at the site. Typically, CRAs cannot use the local site's computer access because of security issues—that is, the CRA cannot use the CRC's password to log on to the site computer.

Solution: The CRA needs to be provided with workspace at the site that has easy access to subject medical records as well as to a high-speed Internet line or wireless router for use with the CRA's laptop computer. To address this need, some sponsors provide funds for sites to install a high-speed line when only dial-up access is available.

The greatest opportunity for enhanced trial efficiency using EDC occurs when the data center is able to integrate the eCRF system with the other critical data systems typically used in clinical trials. This includes the Interactive Voice Response System (IVRS) used for randomization, the electronic system for reporting serious adverse events (eSAE reporting), as well as the identification of subjects whose data may require review by a clinical endpoint committee. The integration of these and other systems should reduce the work required to reconcile discrepant data sets and reduce the number of queries sent to investigative sites.

Figure 14.5 Sample eCRF Screen Shot

Regulations Regarding Electronic Data Capture

The regulations in 21 CFR 11 require procedures and controls when EDC is used. These include validation of the systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.[7] Access must be limited to authorized individuals, and there must be protection of records to enable their accurate and ready retrieval throughout the record retention period.[8] A complete listing of the regulatory requirements for controls for closed systems can be found in 21 CFR 11.10. At the completion of the clinical trial, the local site is provided a CD or DVD that contains all of their subjects' data.

Electronic Signatures

When submitting records electronically, there are regulatory provisions made for the submission of electronic signatures. These include:

- Each electronic signature shall be unique to one individual and will not be used by, or reassigned to, anyone else.
- Persons using electronic signatures shall certify that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.
- Certification of signatures will be signed with a traditional handwritten signature and submitted to the FDA in paper form.
- Persons using electronic signatures will upon request provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.[9]

With ever-changing technology and the widespread availability of high-speed Internet access and computers, electronic records and signatures have become more widely used and trusted.

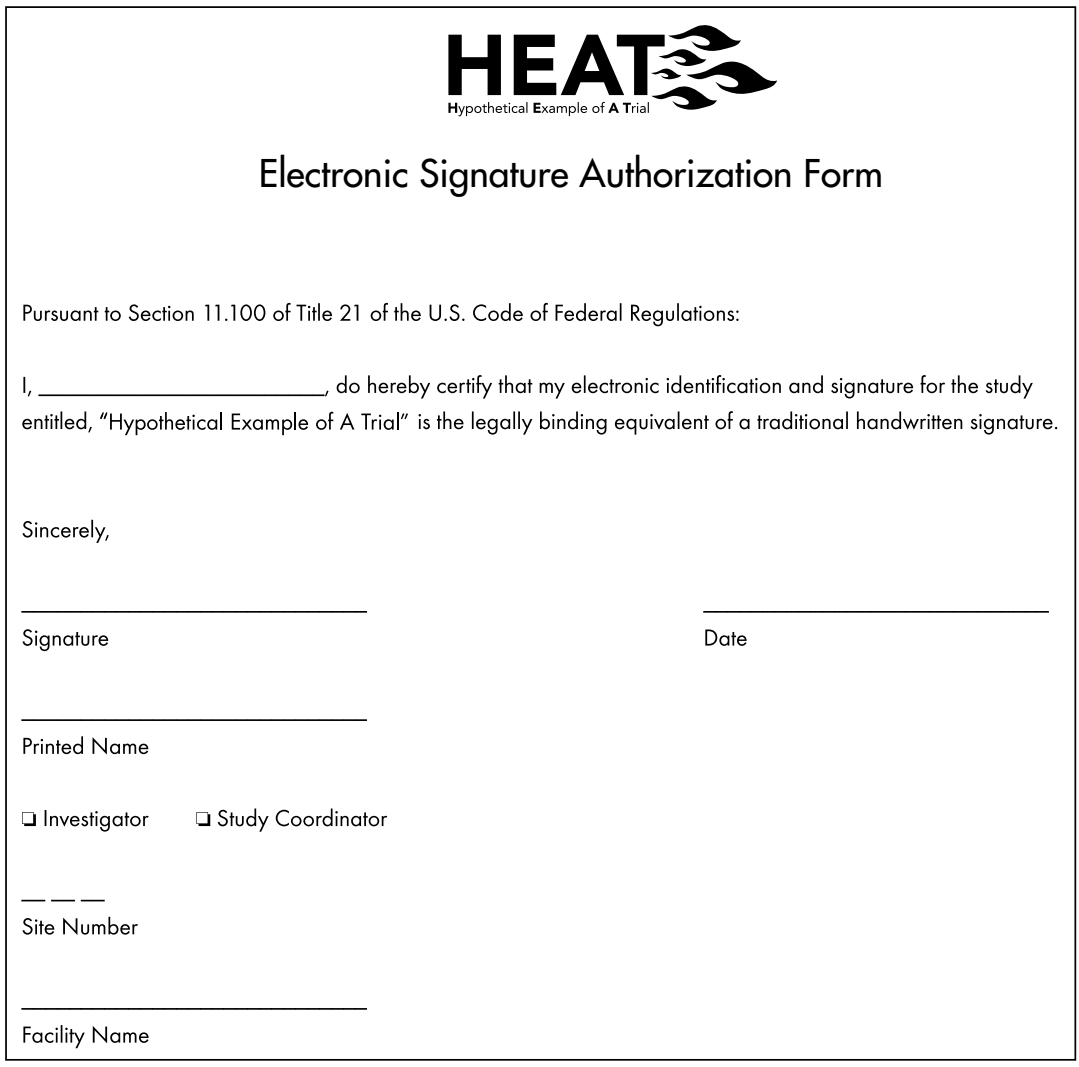
Types of Data Forms

A number of data forms are listed below. This list does not include all forms used in clinical trials, but does include many commonly used forms. These may be provided on paper or may require electronic completion.

Enrollment Form

Enrollment Forms are typically separate worksheets used to identify and screen potential subjects. The Enrollment Form often lists inclusion and exclusion criteria identified in the protocol, and may be used to check off eligibility criteria as you screen subject records. Some

Figure 14.6 Sample Electronic Signature Form



HEAT
Hypothetical Example of A Trial

Electronic Signature Authorization Form

Pursuant to Section 11.100 of Title 21 of the U.S. Code of Federal Regulations:

I, _____, do hereby certify that my electronic identification and signature for the study entitled, "Hypothetical Example of A Trial" is the legally binding equivalent of a traditional handwritten signature.

Sincerely,

_____ _____

Signature Date

_____

Printed Name

❑ Investigator ❑ Study Coordinator

— — —

Site Number

_____

Facility Name

sponsors require the Enrollment Form to be submitted to the data center, while in other trials it may be kept at the site and used as a reference and a confirmation of the screening and enrollment process.

Case Report Form

The CRF is the primary data form that records an enrolled subject's course of events. The CRF often includes information about the subject's medical history and pre-existing conditions, in addition to events that occur during and after treatment. The CRF may range in length from a single page to more than 100 pages, depending on the complexity and requirements of a trial.

Figure 14.7 Sample Enrollment Form

HEAT
Hypothetical Example of A Trial

Protocol-Study #: ___ ___ ___ (protocol number) – ___ ___ ___ (site number) Subject's Initials: ___ ___ ___ (first middle last)

Enrollment Form

Inclusion Criteria – Questions 1–4 must be answered Yes.

1 **Did the subject complete A-Phase?** ☐ Yes ☐ No

2 **Is the subject's total cholesterol level <250 mg/dL (6.4 mmol/L)?** ☐ Yes ☐ No

3 **Did the subject have any of the following clinical and or angiographic risk factors?** ☐ Yes ☐ No

a. Age ≥ 70 years
b. Diabetes mellitus *(Type 1 or Type 2)*
c. Documented history of prior MI, prior CABG, prior PCI or known CAD *(≥ 75% stenosis)* on prior angiogram
d. Evidence of LV dysfunction
e. History of peripheral or cerebral vascular disease
f. Additional angina with dynamic ST changes
g. A positive cardiac marker
h. A positive discharge functional study
i. Minimal coronary disease burden defined as: ≥ 2-vessel coronary artery disease or single-vessel disease not revascularized

4 **Was the subject clinically stable* within 120 hours of HEAT enrollment?** ☐ Yes ☐ No

***Free from the following events for 12 consecutive hours:**

a. Chest discomfort at rest
b. Hemodynamic instability
c. Ischemic events
d. Arrhythmic events
e. Miscellaneous events including: *stroke, pulmonary embolus, sepsis, and acute pericarditis*

Exclusion Criteria – Questions 5–8 must be answered No.

5 **Further percutaneous revascularization procedures planned within the first two weeks after randomization into HEAT?** *(i.e., PTCA/PCI)* ☐ Yes ☐ No

6 **No significant coronary artery disease** *(no lesion ≥ 75%)* **or single-vessel disease confirmed by diagnostic angiography, in the absence of a qualifying risk factor, when PTCA/PCI is planned either prior to or after randomization is planned?** ☐ Yes ☐ No

7 **CABG planned or scheduled either during or after index hospitalization, or after randomization?** ☐ Yes ☐ No

8 **Inability to comply with HEAT procedures?** ☐ Yes ☐ No

Enrollment

Study Drug ID#: 5 ___ ___ ___ ___

Enrollment date and time: ___ (day) /___ (month) /___ (year) ___ (00:00 to 23:59)

US SITES ONLY, **provide your fax #:** (___ ___ ___) ___ ___ ___ – ___ ___ ___ ___

[data management use only]

Confirmation fax sent to site: ☐

Date: ___ (day) /___ (month) /___ (year)

Complete this form for ALL SUBJECTS and fax within 24 hours.

US: Fax to 919-123-4567 · Non-US: Fax to your local CRA

HEAT Enrollment Worksheet, page 1 of 1

Follow-up Form

In some trials, follow-up forms are separate from the CRF and are used to record data at specified times after study enrollment; for example, at 6 months or 1 year after study enrollment. Many trials include these data as part of the CRF and do not create separate forms for follow-up data.

Figure 14.8 Sample Follow-up Form

HEAT
Hypothetical **E**xample of **A** **T**rial

Subject Study Number: ___ ___ ___ - ___ ___ ___ [site no.] Subject Initials: ___ ___ ___ [first middle last]

6-Month Follow-Up

EuroQoL Thermometer and Questionnaire (form located in the HEAT forms file)

Have the subject complete the EureQoL Thermometer and Questionnaire *(2 pages)* at the start of the Follow-up Visit AND send in with the subject's Case Report Form.

Subject Consent

Has the subject withdrawn consent since the last visit? ☐ No ☐ Yes → **If Yes, date:** __ __ /__ __ __ /__ __ __ __ [DAY / MONTH / YEAR]

Complications/Events (since last visit)

Complication/Event:	No	Yes	If Yes...
Death:	☐	☐	**Date:** __ __ /__ __ __ /__ __ __ __ [DAY / MONTH / YEAR] → Complete the Death Notification **Cause of death** *(check one)*: ☐ Unknown ☐ Sudden cardiac death *(within 2 hours of symptoms)* ☐ Myocardial infarction ☐ Congestive heart failure ☐ Stroke ☐ Other *(specify)*: _____
Congestive heart failure:	☐	☐	**Worst NYHA Classification in the past 6 weeks** *(check one)*: ☐ I ☐ II ☐ III ☐ IV
Atrial fibrillation/ flutter:	☐	☐	**Did the subject present with atrial fibrillation or atrial flutter?** ☐ No ☐ Yes
Myocardial infarction:	☐	☐	**Date:** __ __ /__ __ __ /__ __ __ __ [DAY / MONTH / YEAR]
Angina:	☐	☐	**Worst CCSC Classification in the past 6 weeks** *(check one)*: ☐ I ☐ II ☐ III ☐ IV
Stroke:	☐	☐	**Date:** __ __ /__ __ __ /__ __ __ __ [DAY / MONTH / YEAR]

Physical Exam

Weight: ___ ___ ___ lbs **Blood pressure** *(sitting)*: ___ ___ ___ [systolic] / ___ ___ ___ [diastolic] mmHg

Cardiac Medications (currently taken by subject)

ACE inhibitors:	☐ No	☐ Yes	**Calcium channel blockers:**	☐ No	☐ Yes	**Propafenone:**	☐ No	☐ Yes
Amiodarone:	☐ No	☐ Yes	**Carvedilol:**	☐ No	☐ Yes	**Sotalol:**	☐ No	☐ Yes
Angiotensin II receptor blockers:	☐ No	☐ Yes	**Digoxin:**	☐ No	☐ Yes	**Quinidine:**	☐ No	☐ Yes
Aspirin:	☐ No	☐ Yes	**Diuretics:**	☐ No	☐ Yes	**Warfarin:**	☐ No	☐ Yes
Beta blockers:	☐ No	☐ Yes	**Nitrates:**	☐ No	☐ Yes			

Signature

This signature acknowledges review and approval of the data recorded for this Follow-up Visit.

Responsible investigator's signature: _____ **Date:** __ __ /__ __ __ /__ __ __ __ [day / month / year]

HEAT CRF, page 1

Serious Adverse Event Report Form

Serious Adverse Events (SAE) Report Forms are used to collect data pertinent to the occurrence of events that require expedited reporting to the FDA by the sponsor. SAE Report Forms must be reviewed and signed by the investigator, giving special attention to the description of the event and the relationship between the study treatment and the event. The sponsor, data center, or drug safety group will provide trial-specific SAE forms that should be used to report SAE data. Data recorded on the final SAE forms should also be reported verbatim on the subject's CRF. Refer to Chapter 6 for additional information on SAEs and general reporting requirements.

Subject-Completed Forms

Questionnaires, charts, and diaries are examples of subject-completed forms. Typically these forms are completed by subjects without input from study personnel to avoid "leading" the subject to a certain response. Once the subject completes these forms, sites may be required to enter the responses onto a separate data form, or directly submit the original document completed by the subject. In some trials, subjects may enter responses into an electronic diary such as a cell phone or other device. Such data are sometimes referred to as *patient-reported outcomes* (PRO), or, when collected by means of electronic devices, as *electronic patient-reported outcomes* (ePRO).

Corrections to data

Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trails should be maintained); this applies to both written and electronic changes or corrections [see section 5.18.4 (n)]. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.
[ICH E6: Guideline for Good Clinical Practice: item 4.9.3]

Correct the Data

Sometimes, original data recorded on data forms may require correction. You may discover an error yourself and need to make a correction before the data form is sent in or monitored; alternatively, when the CRA reviews data forms during source document verification, errors may be identified and changes required. Corrections may also be needed after forms are sent to the data center for data entry. Computerized checks may identify blanks, out-of-range responses, discrepancies, or inconsistencies necessitating review and/or correction.

In all cases where data need to be changed from the original entry on a paper form, a single line should be drawn through (but should not obscure) the original entry, the corrected data written in the area immediately adjacent, and the change initialed and dated. **Under no circumstances whatsoever** should data on paper CRFs ever be erased or covered with correction fluid. (See example on page 304.) Electronic CRFs maintain an electronic audit trail of all data changes.

Figure 14.9 Example of a Subject-Completed Form

Subject Study Number: ___ ___ ___ – ___ ___ ___ [site no.] Subject Initials: ___ ___ ___ first middle last

HEAT
Hypothetical Example of A Trial

EuroQoL Questionnaire

EuroQol Questionnaire

By placing a check ☑ in one box in each group below, please indicate which statement best describes your own health state today.

Mobility:

☐ I have no problems in walking about
☐ I have some problems in walking about
☐ I am confined to bed

Self-care:

☐ I have no problems with self-care
☐ I have some problems washing or dressing myself
☐ I am unable to wash or dress myself

Usual activities *(i.e., work, study, housework, family or leisure activities):*

☐ I have no problems with performing my usual activities
☐ I have some problems with performing my usual activities
☐ I am unable to perform my usual activities

Pain/discomfort:

☐ I have no pain or discomfort
☐ I have moderate pain or discomfort
☐ I have extreme pain or discomfort

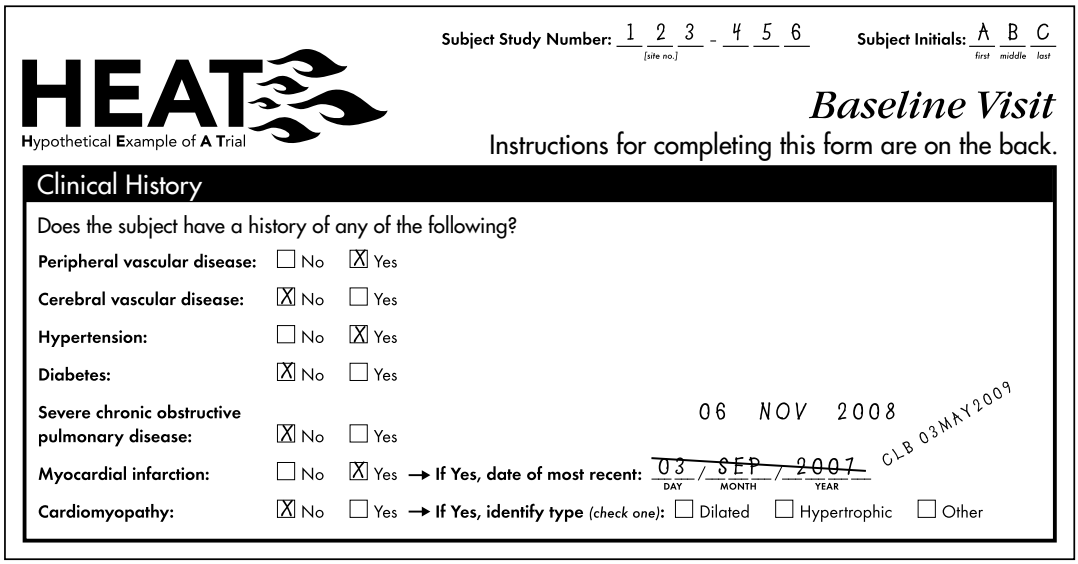
Anxiety/depression:

☐ I am not anxious or depressed
☐ I am moderately anxious or depressed
☐ I am extremely anxious or depressed

Data Form Edits and Queries

Missing values, incorrect information, and inconsistent data all represent potential problems for the data analysis process. Therefore, when the data center receives and enters submitted data, entries that need to be edited or queried are identified. Values for missing responses will be requested, and data that are outside the anticipated range of answers will be explored or confirmed. Some data centers separate data questions into edits and queries; others do not make this distinction.

Figure 14.10 Method to Correct Original Data on Paper Data Forms



HEAT
Hypothetical Example of A Trial

Subject Study Number: 1 2 3 - 4 5 6 [site no.] Subject Initials: A B C (first middle last)

Baseline Visit

Instructions for completing this form are on the back.

Clinical History

Does the subject have a history of any of the following?

Peripheral vascular disease:	☐ No	☒ Yes	
Cerebral vascular disease:	☒ No	☐ Yes	
Hypertension:	☐ No	☒ Yes	
Diabetes:	☒ No	☐ Yes	
Severe chronic obstructive pulmonary disease:	☒ No	☐ Yes	06 NOV 2008 CLB 03MAY2009
Myocardial infarction:	☐ No	☒ Yes	→ If Yes, date of most recent: 03 (DAY) / SEP (MONTH) / 2007 (YEAR)
Cardiomyopathy:	☒ No	☐ Yes	→ If Yes, identify type (check one): ☐ Dilated ☐ Hypertrophic ☐ Other

Data Edits

Data edits are questions or issues identified by the data center that can be answered at the data center without sending a query to the site. An example of an edit is the insertion of a middle initial in the subject identifier when it is missing on a single data form page. Data edit changes are made at the data center and the site is notified (rather than queried) about the change. When you agree with the edit, no response is required. However, if you disagree with the change, it is your responsibility to respond to the data center. The data center should provide specific directions pertaining to data edits and the required action of site study personnel.

Data Queries

Data queries are questions that require the CRC to provide answers or clarification. Queries usually fall into one of three categories: 1) data fields that are blank; 2) data that are outside of a prespecified range; and 3) data that are inconsistent with other data recorded on the forms.

If you are entering data electronically, these types of issues will be identified for your immediate response. You will be prompted to

complete all blanks and confirm out-of-range responses before submitting the electronic forms.

Blank Data

To avoid unnecessary queries about blank data fields, the sponsor or data center will provide *data conventions*. For example, when a procedure or test was not performed or there are no data to answer the question, you may be instructed to record "ND" in the field. When a data question is not applicable to a particular subject or the data are not available, you may be asked to record "NA."

Data Outside of a Prespecified Range

Queries will be generated for data that fall outside of a prespecified or expected range. For example, if a subject's hematocrit level was recorded as 4.3 instead of 43, a query would be generated based on the expected range for hematocrit values in the study. Because ranges are established to cover both normal responses and responses slightly outside the normal range, some queries may be generated for data that were correctly recorded on the form. For example, if the prespecified range for hematocrit values is established as 33–47, a hematocrit value of 30 may be queried even if it is correct.

Inconsistent Data

Responses that are inconsistent with data reported elsewhere on the form will be queried. An example of inconsistent data is the reporting of a medication that was discontinued due to hypotension on one data form, despite the field for reporting an instance of hypotension being checked "no" elsewhere in the CRF.

Response to Data Queries

Most data forms generate one or more queries that require you to review the subject records and data forms to determine whether the data are correct as recorded, or whether they need to be changed. A response to each query should be made in a timely manner following the instructions provided. If you determine that the original entry was incorrect, you can complete the data query form to provide the correct information. However, if you determine that the original data were correct, then you will need to confirm the original value reported. To facilitate the query process, you may want to keep a copy of source documents – such as laboratory or test results – with your copies of the completed data forms or in the subject's study file.

The data center should provide instructions as to whether data changes should be submitted electronically, recorded on a specified form (such as a data query form), or directly onto your copy of the CRF. Instructions for correcting data must be carefully followed so that

Figure 14.11 Example of a Data Query Form

Data Clarification Form

Query initiated by:

❑ Clinical Research Coordinator (CRC)

❑ Clinical Research Associate (CRA): _____ Subject Study Number: __ __ __ - __ __ __ Subject Initials: __ __ __

Discrepancy Source	Current Entry	Corrected Entry	FOR OFFICE USE ONLY
CRF Page # 1 Section: Demographics Item #: 6 Weight	SAMPLE 065 lb	065 kg	Database updated: _____/_____/_____ day mon year _____ Initials
CRF Page #_____ Section: _____ Item #: _____			Database updated: _____/_____/_____ day mon year _____ Initials
CRF Page #_____ Section: _____ Item #: _____			Database updated: _____/_____/_____ day mon year _____ Initials
CRF Page #_____ Section: _____ Item #: _____			Database updated: _____/_____/_____ day mon year _____ Initials

Please SIGN, DATE, SCAN, and EMAIL this form to: Data Management—HEAT trial team
HEATdata@datamanagement.org

Or FAX to: North American sites: (919) 123-4567
All other sites: Contact your CRA

_____ _____

Signature (PI or CRC) *Date*

Maintain original and fax confirmation with the CRF Page ___ of ___

Manual DCF

your data forms exactly match those at the data center. Keep a copy of all corrections and query forms with the original data forms so a record or "audit trail" of changes is available. This audit trail provides a clear link between the original data and the final data, with documentation of who made the change and when the change occurred.

Submit the Data

Sponsors may require that data be submitted by mail, courier, fax, or electronically via computer or other devices. The timely submission of data is critical to meeting deadlines for data entry and analysis established by the sponsor. Instructions regarding when to submit subject data are usually provided by the sponsor or data center personnel.

Submitting Data Electronically

Some sponsors require electronic data entry by the site study personnel; as the relevant technology becomes increasingly sophisticated, reliable, and widespread, the proportion of studies using site-based electronic data entry is likely to continue to grow. This system of "remote data entry" allows data to be directly entered into predesigned screens at the site, bypassing the process of submitting paper copies of data forms. Data entry programs may be set up to accept only entries that fall within the protocol-specified parameters and reject entries that fall outside expected ranges. An advantage of remote data entry is the reduced time from data entry at the site to the time that data is received at the data center. Security systems, including passwords that provide access to data fields, are used to assure the integrity and confidentiality of the data, and to ensure that previously entered data are not deleted or changed. When using remote data entry, it is recommended (although not required) that a paper copy of data forms be printed and kept at the site. The Electronic Record Rule found in 21 CFR 11 requires an electronic back-up of documents. The trial sponsor or data center should provide sites with specific instructions on processes required for data back-up.

Submitting Data Forms

- *SAE Report Forms* are usually due within 24 hours of the investigator learning of the reportable event. SAE Report Forms may be faxed or submitted electronically in order to provide data to the sponsor or drug safety group within the appropriate timeframes.
- *CRFs* may be submitted once they are completed or at specified intervals, such as when multiple follow-up visits occur over a long period of time. When CRFs require source document

verification at the site before being submitted to the data center, the CRA may be responsible for submitting the CRF. In some trials, the CRF is submitted to the data center without on-site source document verification.

- *Follow-up Forms* may be due weeks, months, or even years after the subject has completed study treatment. When Follow-up Forms are used, it is important to collect accurate contact information (telephone, address, name and contact information of relative or friend not living with subject) so that the subject can be located at the appropriate timepoints.

Store/Archive the Data

Record retention regulations and guidelines in 21 CFR 312.62(c), 21 CFR 812.140(d), and in ICH E6 section 4.9.5 require essential documents of a study to be retained for a minimum of 2 years after the approval of a marketing application; if no marketing application will be submitted, records must be kept for 2 years after the investigation of the product is discontinued. Maintaining and providing access to the records for inspection is the responsibility of the principal investigator (21 CFR 312.62 and §312.68). Some sponsors require a longer period of record retention that may last up to 15 years for international trials. The safest and best plan is to contact the sponsor to determine the appropriate period to keep your records.

In trials where EDC is used, sites may be provided with a CD or DVD containing all subject data from the site; this should be filed with the site study file. In trials using paper data forms, all subject data forms must be kept as part of the site study file.

You may need to store data forms off-site because of space constraints in your office. When this is required, information should be kept in your office indicating the location of off-site storage.

Record Retention Period in Canada

In Canada all clinical trial records must be maintained by the site and/or the sponsor for 25 years.

Record Retention in Device Trials

An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.
[21 CFR 812.140(d)]

Source Document Verification of Clinical Trial Data

Source documents must contain information that substantiates the data recorded on the subject data forms. An exception to this includes forms or questionnaires that are completed by subjects and not transcribed by study personnel onto separate data forms.

One of the primary responsibilities of the CRA during an on-site visit is to verify that data recorded on the data forms can be confirmed when compared to the source documents.

1 When erroneous data are noted on a data form or conflicting information is found in source documents, the CRA will identify these for discussion with the CRC.
2 When data recorded on forms are determined to be incorrect, the CRA will provide the CRC with instructions on the method and process for correcting them.
3 When conflicting data exist within the source documents, the reasons why specific data were recorded on the forms should be documented and kept in the study file. For example: when surgery information is reported in three separate entries – in the physician progress notes, in a surgical operative note, and in the discharge summary – it is not uncommon for minor differences to be noted. If the CRC or PI knows that the most accurate and consistent information is printed in the operative note, data from that source should be recorded on the data forms and a note documenting this placed in the study file.

In some trials, source documents are submitted to the sponsor or data center for in-house source document verification. This may be necessary for the review and evaluation of SAEs or for confirmation of endpoints. Queries similar to those generated on-site by the CRA (based on a review of the medical record) may be sent to the site for review and response.

Release of Protected Medical Information

In some trials, the subject may be admitted to another hospital or treated under the care of another physician. In these situations, it may prove challenging to obtain the subject's medical information. If subjects are likely to visit another physician or hospital, and information from those records is required in the CRF or on Follow-up Forms, it will be important to set up a system of medical record retrieval before study enrollment begins.

This can be accomplished by establishing a contact in the physician's office or medical record department of the subject's clinic or medical institution. You will need to determine the proper procedure for obtaining medical records from the other institutions, and obtain answers to the following questions:

- Is there a specific form that the subject needs to sign to give you permission to obtain a copy of the records?
- Are records available for an on-site review?
- Does the institution charge a fee for photocopying records?

Confidentiality of Clinical Trial Data

Each clinical trial creates a system for identifying subjects on the data forms. Typically, a number is assigned to the subject at the beginning of the study and is used in conjunction with the subject's initials on all forms and communication regarding the subject. Information that identifies a subject by name or provides other specific details related to subject identity should not be submitted to the sponsor or data center. When source documents such as ECGs, x-ray reports, laboratory results, and other records are submitted to the sponsor, data center, or event review committee, the subject's name and other identifying information should be crossed out or obliterated. The assigned study number and subject initials should be the only subject identifiers on the documents. Because CRAs as well as auditors and inspectors are authorized by regulations to have access to the subject's medical records on-site, it is not possible to maintain complete subject confidentiality. However, the data forms should all be de-identified and all source documents submitted for review should have the subject's name and any other identifiers completely marked out.

Confidentiality of Subject Records

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.
[ICH E6 section 2.11]

Endpoint Adjudication

Interpreting endpoint data is crucial to the analysis and reported results of a clinical trial. While investigators should follow the protocol-specified definitions when completing data forms, there may still be some variability in how investigators interpret the clinical experiences of study subjects. Some sponsors establish an impartial group of clinicians to review endpoint data, eliminating investigator variability. This group of clinicians, sometimes called a *clinical endpoints committee* (CEC), is responsible for reviewing data forms and source documentation for specified events to determine whether an endpoint has been reached based on pre-established criteria. In the instance of a stroke, for example, the investigator may be required to send in x-ray and/or MRI reports and films for the CEC to review. Using criteria established in the protocol, the committee will review the films and reports, written medical records, and subject symptoms to make a decision independently of the site investigator about whether the endpoint was met. When the study results are published, a description of the process for reviewing and adjudicating endpoints is included.

Need for Endpoint Adjudication

The field of cardiology provides an example of the need for endpoint adjudication in the case of determining whether a myocardial infarction (MI) has occurred. Several trials, including PURSUIT, GUSTO-IIb, and IMPACT-II, used "nonfatal MI" as an endpoint.[10] MIs were diagnosed by physicians based on cardiac enzymes, ECGs, and relevant clinical information. Despite the fact that "MI" was defined in the protocols, there were still discrepancies between MIs assessed by the site investigators and those identified by CEC review (the CEC identified more MIs than the site investigators). It is thought that the basis for this disagreement was the reluctance of physicians to diagnose an MI in patients they were treating, especially when there were only mild elevations of cardiac enzymes, or when the cardiac enzyme elevations occurred after a procedure had been performed.[11]

References

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2 Part 164.501 Security and Privacy; Subpart E – Privacy of Individually Identifiable Health Information
3 OCR HIPAA Privacy. http://www.hhs.gov/ocr/hipaa/guidelines/research.pdf
4 45 CFR 164.512(ii)(f)(g)(h)
5 OCR HIPAA Privacy. http://www.hhs.gov/ocr/hipaa/guidelines/research.pdf
6 http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf
7 21 CFR 11.10(a)
8 21 CFR 11.10(c)(d)
9 21 CFR 11.100(a)(c)(1)(2)
10 PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (Eptifibatide) Therapy), GUSTO-IIb (Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes), and IMPACT-II (Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis)
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15 Global Health and International Trials

In this Chapter

- Current global health concerns
- International trials
- Ethical and scientific concerns

"Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world."

Louis Pasteur (1822–1895), French chemist and microbiologist who advanced the modern germ theory of disease, created effective vaccines for rabies and anthrax, developed the process known as "pasteurization" to remove bacteria from milk

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

We live in a global village where all regional and national actions have global consequences and are affected by global events. Medical product development and clinical trials are part of this global environment. Although only 50 years ago most pharmaceutical companies were regionally or nationally based, recent decades have seen a wave of consolidation and mergers among the industry, and many pharmaceutical companies now have a truly global presence. This globalization of pharmaceutical companies has naturally led to an increasing internationalization of clinical trials.

International Clinical Trials

Pharmaceutical companies often test new medical products in clinical trials that involve investigators from clinical sites in a wide range of countries. The inclusion of a large number of sites allows trials to be conducted more quickly, making a more rapid approval for marketing possible. Moreover, many trials require large numbers of subjects to identify treatment effects; the involvement of many sites around the world facilitates enrollment of subjects within a reasonable period.

Successful international trials usually rely on regional coordinating centers to manage sites within a geographic area. The use of these centers avoids many of the problems associated with collaborations across different time zones; facilitates awareness of sensitivities and problems unique to a region, language, or culture; and helps to develop networks for future clinical trials. Rather than using one data center at the sponsor location, the sponsor may employ multiple data centers that are regionally located; for example, investigative sites in South America may be required to submit data to a data center that serves that continent, while European investigators participating in the same trial submit data to a center within Europe. All data centers associated with the trial use the same data management software programs for seamless data integration and analysis.

Recently, the number of multi-site, multi-national clinical trials being conducted, particularly in developing and newly developed countries, has increased substantially. Countries that previously had not participated in clinical research are now actively engaged in the search for answers to global health care questions. New technologies and widespread access to the Internet have made it possible to communicate easily with colleagues scattered across the globe and have enabled the collection and distribution of enormous amounts of data.

This globalization of clinical trials holds appeal for pharmaceutical companies seeking access to large patient populations and lower research costs when testing new products. Access to large populations in China and India holds promise for faster subject recruitment and study completion, and the lower salaries of physicians and the research staff in developing countries leads to significant cost savings for product sponsors. Moreover, in many countries with mature medical systems, patients are uniformly treated early in the course of their diseases as part of patient and physician preference, which may confound study results. On the other hand, countries with emerging economies often will not have such treatment biases and can recruit newly diagnosed patients who are "treatment-naïve" (i.e., having had little or no prior treatment for the disease or condition under study).

Ethnic and Racial Differences

Many trials of investigational products are conducted in populations that are, for the most part, racially or ethnically homogeneous, which makes it difficult to predict accurately the efficacy and safety of the products when they are administered to different populations who may have genetically-determined differences in their response to the treatment. In order to test products in various ethnic or racial groups to determine differences in dosing and side effects, trials of marketed products increasingly are being conducted in more diverse populations. Since genetic diversity is not often considered in the design of early studies intended to support a marketing application, these postmarketing trials are important mechanisms for identifying differences in racial and ethnic response to treatments.

A good example of why such trials are needed is provided by the history of clinical experience with carbamazepine, a drug approved in the United States for the treatment of epilepsy, mania/bipolar disorder, and neuropathic pain. Stevens Johnson syndrome (SJS), a serious and potentially life-threatening disease of the skin and mucous membranes, was initially thought to be a rare side effect of carbamazepine treatment. However as the marketed drug was administered to more patients, SJS was found to be significantly more common in patients with the human leukocyte antigen (HLA) allele, HLA-B*1502. This allele is found almost exclusively in people of Asian descent, including South Asian Indians. The FDA now recommends genetic testing

Large International Studies

The timely completion of many trials requires the collaboration of hundreds of investigators from many different countries working together. The major goal is to accrue large numbers of subjects in the shortest time possible. The following cardiology trials were conducted in the mid-1980s through the 1990s using regional networks of investigators. Large numbers of subjects were required to detect statistically significant differences in treatment groups.

- GISSI 1 – Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (Italian Group for the Study of Streptokinase in Myocardial Infarction). A study of 11,712 patients to evaluate the efficacy of a thrombolytic treatment (streptokinase) on in-hospital mortality of patients who had an acute myocardial infarction.
- ISIS 1 – (International Study of Infarct Survival). A trial of atenolol in more than 16,000 patients with a suspected myocardial infarction.
- GUSTO 1 – (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries). A study to evaluate infarct vessel patency on long-term survival in more than 41,000 patients with myocardial infarction.

Genetic Link to Warfarin Dosage?

2009 – Investigators at the National University Hospital in Singapore are participating in a clinical trial on ethnic pharmacogenetics using a formula that calculates warfarin dosing based on a subject's genetic makeup. The investigators hypothesize that precise dosing will prevent bleeding events caused by excessive dosage as well as loss of therapeutic effects from too low a dose. Study dosing is based on age, weight, and the way in which two identified genes control the processing of warfarin. In a group of 100 patients, initial findings indicate that Indians were found to require a dose about 0.5 mg higher than the 5 mg dose usually prescribed, while Chinese and Malays needed only about half the usual dose, a difference believed to be due to variations in genetic makeup among the populations.[2]

for HLA-B*1502 before starting treatment with carbamazepine; patients who test positive for the allele should not be treated with the drug.[1]

Because of these genetic differences, which affect how different populations respond to medicinal products, some national regulatory authorities now require in-country testing of products before providing approval for marketing. For example, Japan and Taiwan require "bridging" studies to identify the safety and efficacy of products studied and approved elsewhere, which typically delays local approval for marketing and use. In an effort to overcome these delays, Japan and Taiwan are now seeking to become involved in simultaneously-conducted clinical trials.

Ethical Issues and Cultural Sensitivities

In addition to the regulatory aspects of international trials, there are issues surrounding the ethical conduct of research in developing countries, as well as cultural sensitivities that may be unique to particular countries or ethnic groups. Investigators and sponsors must be aware of cultural differences before designing a study that might inadvertently impose attitudes from the sponsoring country on research subjects. Major concerns in developing countries arise from fears of exploitation by pharmaceutical companies based in countries with developed economies. Ethical questions pertaining to issues of beneficence, autonomy, and justice may all arise in the course of such studies: Is it appropriate to conduct research in countries where the research subjects are not likely to benefit from the marketing of the product being tested? Is it ethical to test a drug in a country with a high level of poverty if the population will not be able to afford the drug after marketing? What is the standard of care that should be applied to subjects in an international trial – is the local standard of care adequate?

These issues are highlighted by the Pfizer Corporation's study of the antibiotic trovafloxacin (marketed as Trovan) during a 1996 epidemic of bacterial meningitis in Kano, Nigeria. In the Pfizer study, Nigerian children were given either trovafloxacin or a dose of a comparator drug. Trovafloxacin was approved by the FDA in 1997 for the treatment of a broad range of infections and was subsequently widely prescribed in the United States; however, after it was linked to several cases of liver failure, the FDA severely restricted its use. Nigerians officials claim that the administration of trovafloxacin was done without the approval of the Nigerian government or the

consent of the subjects' parents and resulted in the deaths of children, leaving others deaf, paralyzed, blind, or brain-damaged.

What were the issues surrounding this trial? Did Pfizer follow ethical and regulatory requirements? Did the Nigerian government understand what to expect from the clinical trial? Was there an unrealistic expectation that the drug would prove successful without any side effects? Was there poor communication between Pfizer and the local investigators and government regulators? In July 2009 Pfizer settled the Nigerian lawsuit with an agreement to underwrite $30 million in health-care initiatives, provide $10 million to Kano to cover legal costs, and pay as much as $35 million to study participants. While Pfizer denies any wrongdoing or liability and claims that the study was conducted ethically and with the full knowledge of the Nigerian government,[3] mistrust remains. Suspicion stemming from this study has led many Nigerian parents to refuse polio immunization for their children.[4] This incident, just one example of problems encountered when trials are conducted by a sponsor external to the country, has contributed to increasing mistrust on the part of developing countries toward medical companies in the developed world.

Cross-cultural sensitivities must be considered when designing a trial with multinational subjects. For example, many Western cultures expect physicians to provide patients and research subjects with specific health care information, including information regarding terminal illnesses, death, and dying. However, it is important to know that in some cultures, it is not considered appropriate for physicians to directly discuss this information with patients. Families may insist that such discussions be avoided; further, custom may dictate that a diagnosis of a terminal disease or cancer be withheld from patients or research subjects to spare them distress or mental anguish. In some cultures and religions, the use of human tissues and organs is not a common or acceptable practice; therefore, requests for blood or tissue samples may not be supported in clinical trials.

Why International Trials Are Important

Many diseases that have a significant impact on developing nations are lower priorities for countries with developed economies, where many epidemic diseases have been eradicated or effectively controlled. A number of organizations and foundations, including the Bill and Melinda Gates Foundation, the United Nations Children's Fund (UNICEF), and the World Health Organization (WHO) are partnering

to speed global research, expand access to life-saving drugs, provide education and resources for disease prevention, and advocate for greater awareness and action. Some of the most urgent issues include the HIV/AIDS epidemic, malaria, tuberculosis, and polio. Many of the clinical trials being conducted on these health problems focus on the development of vaccines, the treatment of opportunistic infections, and measures to prevent disease transmission.

HIV/AIDS

In 2007, an estimated 33.2 million people worldwide were living with HIV/AIDS and each year, an estimated 2.3 million people are newly infected with HIV (more than 6,000 new infections each day). While antiretroviral treatment for HIV has been shown to be effective in increasing the number of immune cells to fight infection and has helped prolong the lives of infected individuals, organizations and scientists are working to develop preventative strategies.[5] Most clinical trials for HIV/AIDS focus on vaccine development: preventive vaccines for HIV-negative persons, and therapeutic vaccines designed to bolster the immune systems of HIV-positive patients. Studies are also being conducted to evaluate the treatment of opportunistic infections and to prevent the transmission of HIV (e.g., prevention of mother-to-child transmission at birth).

Malaria

Malaria, a parasitic disease caused by a variety of protozoan species from the genus *Plasmodium* and spread by mosquitoes, continues to cause hundreds of thousands of deaths each year. In Africa, malaria takes the lives of 2,000 children a day. Although malaria can be treated, people who survive malaria can suffer debilitating consequences, such as mothers delivering low–birth-weight babies and children developing severe anemia. Scientists around the world are partnering to develop vaccines as well as other prevention strategies, such as administering anti-malarial drugs to infants at the same time that they receive routine vaccinations for other childhood diseases. Methods to prevent the transmission of malaria include the distribution of insecticide-treated bed nets and new forms of pesticide spraying.[6]

Tuberculosis

Tuberculosis (TB), a bacterial disease of the lung that can be fatal if not properly treated, continues to be a serious global health

problem. More than 2 billion people worldwide are infected with Mycobacterium, the organism that causes TB. When individuals with HIV develop TB, there can be lethal consequences; people who are HIV-positive and infected with TB are up to 50 times more likely to develop active TB. Multidrug-resistant TB is a form of TB that fails to respond to standard first-line drugs. Resistance can also occur to second-line drugs, resulting in TB that is virtually untreatable.[7] Many of current clinical trials are directed at the treatment of multidrug-resistant TB, as well as the treatment of TB in HIV-positive individuals.

Polio

Polio (poliomyelitis) is a highly infectious viral disease that affects the central nervous system, causing loss of motor control, paralysis, and even death. Following the development of vaccines in the 1950s and 1960s, polio was nearly eradicated in many countries. An aggressive campaign of vaccination led to very low rates of the disease, and surveillance and screening was performed to be sure that the disease did not re-emerge. In 1988, the World Health Organization, along with Rotary International, UNICEF, and the U.S. Centers for Disease Control and Prevention (CDC) formed an alliance to eradicate polio on a global basis. Although the incidence of polio has been reduced by 99 percent, new polio cases continue to be reported. Especially concerning is the identification of new cases in areas that were previously free of the disease. Four remaining countries (Afghanistan, India, Nigeria, and Pakistan) where polio continues to be endemic are the focus of current vaccination efforts.[8] The primary push to eliminate polio is through worldwide vaccination programs, but clinical trials are also being conducted to evaluate combination vaccines, different timing and dosages of vaccines, as well as treatment for fatigue associated with post-polio syndrome.

Clinical trials that focus on these diseases are important not only for reducing the incidence of the diseases, but also for allowing investigators in developing countries to gain expertise in conducting clinical trials to address other health care problems. These trials not only train local investigators, clinical research coordinators, and ethics committee personnel, but also contribute to development of the infrastructure needed to conduct clinical trials. They also help build local networks of investigators and health care providers with the experience and understanding of the products needed to safely prescribe new treatments and monitor patients. In this way, developing countries can become self-reliant in testing new products that will have an impact on their national health care issues.

The Polio Vaccine

Dr. Jonas Salk started his medical research career studying immunology and began research on the poliovirus in 1947. Salk was the first to develop a successful vaccine using a process that inactivated the virus. Testing of the vaccine in clinical trials occurred in the United States and Canada on a massive scale; the result was a dramatic decrease in polio cases in the vaccinated groups. However, there was a problem with the Salk vaccine: because of incomplete inactivation of some virus particles, the vaccine caused 260 cases of poliomyelitis, 10 of which were fatal. This problem was ultimately resolved, resulting in a vaccine that was 70%–90% effective.

Dr. Albert Sabin began testing a live-virus oral vaccine in 1957. The oral vaccine provides long-lasting immunity but cannot be used in people who are immuno-compromised.

Both vaccines are in use today. Scientists are now using recombinant biotechnology to attempt genetic alteration of the poliovirus in attempts to eliminate any possibility of the virus infecting the vaccinated person.[9]

Regulations Resulting from Tragedies

First introduced in 1935, *sulfanilamide* was an effective treatment for bacterial infections. However, the pills were bitter and therefore difficult to swallow, especially for children. To make the drug easier for patients to take, a chemist created a liquid solution in which the sulfanilamide was dissolved. Soon after this sulfanilamide product came on the market, there were reports of 107 deaths after patients, mostly children, ingested the medication labeled "elixir of sulfanilamide." It was then discovered that it was not an elixir (by definition an alcohol solution), but a diethylene glycol solution (diethylene glycol is the principal ingredient in antifreeze; it is highly poisonous). The FDA successfully removed the product from the market and in the following year, the Food, Drug, and Cosmetic Act of 1938 was enacted to require proof of *safety* of new drugs before marketing.

In the late 1950s to early 1960s, an estimated 10,000 babies in Europe and Africa were born with birth defects, including phocomelia (a defective development of the arms and/or legs in which the hands and feet are attached close to the body) to mothers who took *thalidomide* while pregnant. At the time, thalidomide was used in Europe to bring a quick, natural sleep for millions of people, and to give pregnant women relief from morning sickness. Marketing of thalidomide was prevented in the United States by FDA medical reviewer Frances Oldham Kelsey, who had requested additional data because of concerns that chronic toxicity studies had not been conducted for sufficiently long periods, absorption and excretion data were inadequate, and clinical reports were not based on the results of well-designed, well-executed studies.

International Regulations

One of the challenges facing international trials is that studies not only have to comply with local and national regulations, but also with international regulations or guidelines. Various countries historically have had different timelines for developing medical products regulations, often in response to problems caused by drugs. In the United States, a mistake in the formulation of sulfanilamide elixir in the 1930s provided the impetus for the Food, Drug, and Cosmetic Act of 1938, setting up a product authorization process under the FDA. In Japan, medicinal products registration became regulated in the 1950s. In many European countries, experience with thalidomide in the 1960s revealed the potential for harm arising from the use of new synthetic drugs. In many countries, the 1960s and 1970s brought a rapid increase in laws and regulations regarding new medical product safety, quality, and efficacy; at the same time the medical product industry was becoming increasingly international. However, medical product registration remained the responsibility of individual countries and there was significant variability in the regulations and requirements for product marketing approval.

Increasing concern about regulatory variability among countries, as well as increasing concern about ethical standards for research at an international level, precipitated interest in harmonizing research requirements among nations. This led to the International Conference on Harmonisation (ICH) initiative. Representatives from Europe, Japan, and the United States met at the **International Conference on Harmonisation** *of Technical Requirements for Registration of Pharmaceuticals for Human Use* and formed a committee of representatives from participating countries to make recommendations for greater standardization in clinical research, with the goal of reducing or eliminating duplication of testing in various countries. They also sought to reduce or eliminate delays in global drug development, while maintaining safeguards on quality, safety, efficacy, and regulatory obligations to protect public health.[10] The ICH Good Clinical Practice (GCP) guidelines have been adopted or adapted by many countries around the world, contributing to the globalization of clinical trials.

Global Cooperation Group for non-ICH Countries

The Global Cooperation Group (GCG) was initially formed in 1999 as a subcommittee of the ICH Steering Committee to respond to a growing interest in ICH beyond the three original ICH regions (Europe, Japan, and the United States). The original purpose of the GCG was to make information regarding the ICH, ICH activities, and ICH guidelines available to any country that requested this information. In the years that followed, however, there was a growing recognition that simply making the ICH guidelines available to other countries would not translate into their adoption and implementation. Therefore in 2007 the GCG took a more active role in engaging other countries' regulatory agencies to achieve the following goals:

- to reduce country and regional differences in technical requirements that impact on the availability and cost of new medicines;
- to promote international movement of pharmaceuticals that are safe, effective and of high quality;
- to promote the conduct of clinical trials and data collection that meet international standards.

To date, representatives from the following regions now attend the GCG meetings: Asia-Pacific Economic Cooperation (APEC), Association of Southeast Asian Nations (ASEAN), Gulf Cooperation Countries (GCC), Pan American Network on Drug Regulatory Harmonization (PANDRH) and Southern African Development Community (SADC).[11]

In acknowledgment of continuing differences in clinical trials regulations, the Global Cooperation Group (GCG) was formed by the ICH Steering Committee to address harmonization in non-ICH countries. The goal of this group is to encourage and facilitate increasing uniformity of clinical trials regulations among countries.

However, while countries and regions may have different regulatory requirements regarding forms and processes, the actual practice of conducting clinical trials has many universal activities and issues. Regardless of the country in which a clinical trial is conducted, documents must be approved by ethics committees/institutional review boards, informed consent must be obtained, subjects must be enrolled based on protocol-specified eligibility criteria, and protocol-required procedures must be carefully completed.

Concerns

Clinical trials still face significant challenges in developing countries, where the underlying concepts of clinical research may be relatively unfamiliar, the regulations less specific or comprehensive, and the investigators less experienced. A number of related concerns were raised by researchers at the Duke Clinical Research Institute (DCRI) in the 19 February 2009 issue of *The New England Journal of Medicine*.[12]

The first of these concerns relates to the fact that many international studies focus on diseases that are not widely prevalent in the country or region where the research is being conducted, while the tested products are then marketed in wealthy developed countries. Indeed, as the authors note, many studies conducted in developing countries are for conditions such as allergic rhinitis and overactive bladder, rather than for conditions such as tuberculosis or malaria that might be thought more relevant. Subjects participating in such trials in developing countries may not even benefit from the product under investigation, raising serious questions regarding the justice and beneficence of the research.

Second, the regulatory agencies of the countries sponsoring international studies often are given limited information regarding the quality of research sites, the qualifications of investigators, and the nature of subjects available in countries with developing economies. For example, there may be wide disparities in education between physicians and participating subjects; economic issues may have an impact when financial compensation for study participation exceeds the annual salary of the typical subject; and standards of health care and cultural issues may result in limited or nonexistent IRB oversight and a lack of informed consent at many sites. The inaccessibility of remote sites often means that regulatory agencies are obliged to rely on information provided by the study sponsor.

Finally, the DCRI researchers found that many investigators in developing countries were unfamiliar with issues regarding their rights to have access to trial data and to publish study results. This lack of transparency may affect the integrity of data gathered in these international trials.[13]

Future Efforts

Significant changes are on the horizon for the clinical research enterprise. In particular, researchers believe the widespread use of genetic information ("genomics") will be used to predict the efficacy and safety of pharmaceuticals and biologics, allowing therapies to be targeted to groups or even individual patients who are most likely to benefit. This may help identify positive responders early in the drug development process, as well as those patients at greatest risk for developing side effects when uncommon adverse events are identified after marketing. Earlier in this chapter, we noted that genetic testing may allow physicians to more accurately target warfarin therapy. Another example of genetic testing can be seen in patients

with HIV infections being treated with abacavir therapy (a reverse transcriptase inhibitor). Testing for the HLA-B*5701 allele in these patients can help predict persons at increased risk for developing an undesirable side effect known as hypersensitivity syndrome (HSS) and allow health care providers to avoid prescribing the drug to these patients.[14]

Regulatory agencies, in trying to balance the need for early access to potentially life-saving new products with the imperative for ensuring product safety and efficacy, are often criticized for erring on one side or the other. They are thus constantly engaged in assessing strategies for achieving the proper balance. Will an increase in post-marketing clinical trials provide real-life monitoring of product use and identify infrequent or rare side effects that can only be seen with wider use? Will mandatory reporting of product problems, side effects, and malfunction provide additional information for health care providers and patients?

Other high-priority topics of discussion include continued harmonization of clinical trials regulations, conflict of interest concerns, the need for clinical testing in vulnerable populations (especially in children), and safety of volunteers in first-in-man studies.

Tremendous opportunities lie ahead for investigators and sites participating in international clinical trials. Efforts must focus on developing collaborations among regulatory agencies, sponsors, and academic organizations around the world, not only to foster the successful growth of clinical trials, but to ensure that research is done according to essential ethical principles and in compliance with regulations protecting the rights and safety of human research participants.

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Appendices

Appendix A

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA 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 in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy

volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

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The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfillingthis part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime

Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes[1] intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergoreview for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called “experimental” when the terms “experimental” and “research” are not carefully defined.

For the most part, the term “practice” refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.[2] By contrast, the term “research” designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is “experimental,” in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.[3]

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression “basic ethical principles” refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. — Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to “volunteer” or to “protect” them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. — Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children — even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. — Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. — Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their

care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited — for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in

order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence — especially where possible sanctions are involved — urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. — The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term “risk” refers to a possibility that harm may occur. However, when expressions such as “small risk” or “high risk” are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term “benefit” is used in the research context to refer to something of positive value related to health or welfare. Unlike, “risk,” “benefit” is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be “balanced” and shown to be “in a favorable ratio.” The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative

techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations:
(i) Brutal or inhumane treatment of human subjects is never morally justified.
(ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures.
(iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject — or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits.
(v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. — Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only “undesirable” persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

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(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

Nuremberg Code

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

   The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Reprinted from *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181–182.* Washington, D.C.: U.S. Government Printing Office, 1949.

Appendix B

HEAT
Hypothetical Example of A Trial

Consent to Participate in a Research Study: Short Form

Study Name: **HEAT (Hypothetical Example of A Trial)**

Protocol Number XYZ 39-90213

Date: **July 19, 2009**

Sponsor: Pharmaceutical Company, USA

Principal Investigator: _____

Institution: _____

I give my consent to participate in this research study that is being done to compare an investigational clot-dissolving medicine to one already on the market. All the items on the Written Summary have been explained to me in the presence of a witness. These include the background and purpose of the study, the procedures required for the study, possible risks and benefits, alternative treatment if I do not participate, confidentiality of my records, compensation, and the names of those I should contact if I have any questions. It has been explained that it is up to me to decide if I want to participate in the study. If I do participate, pertinent new information will be explained to me while I am in the study. I have had the chance to ask questions and they have all been answered so that I understand. I have been told that a copy of this consent form and a copy of the written summary will be given to me.

_____	_____	__/__/__
Name of Study Participant	*Signature of Study Participant*	*Date*

I have witnessed the summary information being verbally presented to the subject. I confirm that all of the information in the written summary has been completely and accurately explained. The subject was given time to ask questions and the questions were answered so that the subject could understand. The subject voluntarily agreed to participate in this study and signed/marked this consent form.

_____	_____	__/__/__
Name of Witness	*Signature of Witness*	*Date*

HEAT
Hypothetical **E**xample of **A** **T**rial

Written Summary

1 Since your doctor has determined that you are having a heart attack, you are being asked to participate in this research study.

2 Your participation is completely voluntary and if you decide to participate, you may withdraw your consent at any time without jeopardy to your medical care.

BACKGROUND AND PURPOSE OF STUDY

3 This study is being done to see if an investigational clot-dissolving medicine is as good as or better than a similar medicine already on the market, when given to people having a heart attack.

4 By quickly dissolving the blood clot in the arteries to the heart, the blood flow can resume and may reduce the amount of heart damage.

5 Approximately 5000 people in the United States will be enrolled in this study.

PROCEDURES

6 You will be given a dose of either the investigational clot-dissolving medicine or the medicine already in use for people with heart attacks. You have a 50% chance of getting the investigational medicine.

7 The medicine is prepared so that neither you nor your doctors know which medicine you are given.

8 The medicine will be given through your veins over one hour.

9 You will have your blood drawn before the medicine is given and again each morning that you are in the hospital. About 2 tablespoons of blood will be drawn each time.

POSSIBLE RISKS

10 All medicines that dissolve blood clots can cause internal bleeding. This could include bleeding into your brain, causing a stroke, which occurs in less than1% of people who get clot-dissolving medicine.

11 If bleeding is severe, you may need a blood transfusion.

12 There could be side effects that we currently do not know about.

POSSIBLE BENEFITS

13 If you get the investigational medicine, it could prove to be better at dissolving the blood clot and getting the blood flowing back to your heart.

14 The marketed medicine dissolves blood clots in about 70% of people who receive it.

ALTERNATIVE TREATMENT

15 If you are not in the study, you will probably be given the marketed medicine for your heart attack.

CONFIDENTIALITY

16 Information about you and how you responded to the treatment will be recorded on forms but your name and other information identifying you will not be written on the forms.

17 The FDA and other personnel from the company who makes the investigational medicine may review your medical records to confirm the information written on the forms.

COMPENSATION

18 You will not receive money or any other kind of compensation or reward for being in the study.

19 You will receive the clot-dissolving medicine and the blood tests required for this study for free; you or your insurance will be billed for the rest of your hospital charges.

20 If you have an injury because of being in this study, you will receive free medical care for the injury.

CONTACTS

21 If you have any questions about the study, you should call Dr. Knowledgeat (888) 111-2222. If you have any questions about your rights as a participant in a research study, you should call Ms. Answers, the chairperson of the hospital committee that reviews research studies, at (888) 333-4444.

OTHER

22 If your doctor or the company that makes the investigational medicine thinks your health or safety could be harmed if you continue in the study, your participation will be stopped.

23 While you are in the study, you will be told about any new information that might make you change your mind about participating in the study.

SIGNATURES

I confirm that the information in this written summary has been verbally presented to the subject and that consent to participate has been freely given by the subject.

_____
Name of Witness

_____ __/__/__
Signature of Witness Date

_____
Name of Person Obtaining Consent

_____ __/__/__
Signature of Person Obtaining Consent Date

Periodic Monitoring Visit Checklist

Subject Status

___ Discuss subject recruitment strategies
___ Ensure correct randomization procedures and maintenance of study blind
___ Verify the status of all study subjects
___ Confirm enrolled subject eligibility
___ Check consent forms for proper signatures and dates before study enrollment

Study Supplies, Storage, and Accountability

___ Ensure that adequate study drug/device supplies are available
___ Check expiration of study drug/device
___ Ensure the accuracy of receipt and dispensing records
___ Meet with personnel who dispense study drugs/devices to resolve problems
___ Inspect storage facilities (secure with limited access) as appropriate
___ Verify process to calculate dosage and confirm accuracy of preparation; verify proper use/setting of device controls as applicable

Regulatory Issues

___ Check study files to ensure all necessary documents are included (signed protocol page and protocol, amendments, consent form, IRB/IEC approval and correspondence)
___ Ensure continuing IRB/IEC notification/reporting as appropriate to include periodic IRB/IEC renewals, protocol amendments, and safety reports
___ Verify that informed consent procedures are being followed and that a valid consent form is present for each subject
___ Collect any new or revised regulatory documents

Laboratory Issues

___ Review protocol-specific laboratory requirements
___ Review laboratory certificates for current date
___ Ensure proper handling of all laboratory specimens
___ Resolve any problems related to the collection of samples or the performance of local, central, or core laboratories

Responsibilities of Site Study Personnel

___ Review responsibilities of site personnel to determine if changes in personnel or responsibilities have occurred since the last monitoring visit
___ Provide training for site personnel when needed, including new study personnel, changes in study procedures, or a change in the conduct of the study such as a protocol amendment

Serious Adverse Event (SAE) Status

___ Review SAEs that occurred at the site
___ Obtain additional SAE information from site as needed
___ Ensure that all SAEs have been reported accurately and appropriately

Source Document Review/Verification of Data

___ Verify accuracy of recorded data as compared to source documents
___ Review data forms for incorrect data, omissions, and out-of-range variables
___ Review source documents for adherence to protocol
___ If paper data forms are used, collect original copies of completed data forms
___ Generate data queries
___ Obtain responses to outstanding data queries

Outstanding Issues

___ Determine actions to be taken by the site for outstanding or unresolved issues
___ Determine actions to be taken by the sponsor for outstanding or unresolved issues

Meet with PI and CRC

___ Discuss overall progress of trial
___ Discuss new developments affecting subject safety/conduct of trial
___ Discuss outstanding issues and actions to be taken by the site and/or sponsor
___ Sign Site Visit Log

Budget Planning Worksheet—Personnel Time

Estimate the time needed to conduct the study based on the protocol requirements.

Number of subjects your site is expected to enroll	_____subjects
Number of weeks required to enroll all subjects	_____weeks
Estimated number of monitoring visits (or frequency)	_____visits/year
Duration of active subject participation	_____weeks
Duration of follow-up	_____weeks
Estimated time period for data clean-up	_____weeks

Proposed Timeline:	**Date:**
Prepare documents for IRB submission	_____
Start enrolling subjects	_____
Enrollment ends	_____
Last visit of active subject participation	_____
Start of follow-up visits	_____
Complete follow-up visits	_____
Complete data cleaning	_____
Archive documents	_____

Activity	**Allotted Hours/Subject**	**Total**
CRC		
Protocol review		_____
Prepare IRB submission		_____
Attend investigator meeting		_____
Create/modify worksheets/data forms		_____
Conduct educational sessions for clinic staff		_____
Screen and enroll subjects	_____hours/subject	_____
Conduct follow-up visits	_____hours/subject	_____
Process and ship blood samples	_____hours/subject	_____
Data form completion	_____hours/subject	_____
Data queries	_____hours/subject	_____
Communicate with sponsor/PI	_____hours/subject	_____
Monitoring visits	_____hours/subject	_____
Archive study documents at trial end		_____
PI		
Review protocol		_____
Study team meetings	_____hours/week	_____
Communicate with sponsor	_____hours/week	_____
Perform initial screening visit for all subjects	_____hours/subject	_____
Perform follow-up visits	_____hours/subject	_____
Review data forms with CRC	_____hours/subject	_____
Pharmacist		
Prepare study drug and maintain accountability	_____hours/subject	_____
Support Staff		
Request and return medical records	_____hours/subject	_____
Contact subjects re: scheduled follow-up and tests	_____hours/subject	_____
Fax documents/type letters/photocopy documents	_____hours/week	_____

HEAT
Hypothetical Example of A Trial

HEAT Signature and Delegation Log

Sponsor: HEAT	Sponsor: protocol number: 2468-00
Test product: Clotbuster or Placebo	
Investigator name: Address:	Site number: __ __ __

Name of Site Personnel	Role	Signature	Initials	Start Date	End Date	Tasks (indicate using codes below)	PI Authorization (Initials)
	PI						

A. Informed consent
B. Physical examination-**MD only***
C. Inclusion/exclusion criteria assessment
D. Randomize subjects
E. Test product dispensing and accountability
F. eCase Report Form (eCRF) completion and correction
G. Sign-off data queries

H. Vital signs
I. Adverse event interpretation-**MD only***
J. Specimen collection (blood, ECG, etc.)
K. Exam result interpretation (labs etc.) **MD only***
L. SAE reporting
M. Other:_____

Roles
PI: Principal Investigator
SI/Co-I: Sub-Investigator/Co-Investigator
CRC: Clinical Research Coordinator
PH: Pharmacist
Other: _____

* Or licensed practitioner

	Principal Investigator	Signature of Principal Investigator	Date
At end of study, PI must confirm all above information is correct and sign.			__ __ /__ __ __ /__ __ __ __ dd mmm yyyy

HEAT
Hypothetical **E**xample of **A** **T**rial

Screening Log

Site #: __ __ __ Page __ of __

Record information for all subjects screened

Date of Screening	Screening Number	Initials	Sex	Age	Enrolled?	Comments or Reason(s) Not Enrolled (Use codes listed below)
__ __ / __ __ __ / __ __ __ __ (dd mmm yyyy)	__ __-__ __	__ __ __	❑ M ❑ F	❑ ≤ 75 ❑ > 75	❑ Yes ❑ No →	
__ __ / __ __ __ / __ __ __ __ (dd mmm yyyy)	__ __-__ __	__ __ __	❑ M ❑ F	❑ ≤ 75 ❑ > 75	❑ Yes ❑ No →	
__ __ / __ __ __ / __ __ __ __ (dd mmm yyyy)	__ __-__ __	__ __ __	❑ M ❑ F	❑ ≤ 75 ❑ > 75	❑ Yes ❑ No →	
__ __ / __ __ __ / __ __ __ __ (dd mmm yyyy)	__ __-__ __	__ __ __	❑ M ❑ F	❑ ≤ 75 ❑ > 75	❑ Yes ❑ No →	
__ __ / __ __ __ / __ __ __ __ (dd mmm yyyy)	__ __-__ __	__ __ __	❑ M ❑ F	❑ ≤ 75 ❑ > 75	❑ Yes ❑ No →	

Use the following codes to indicate the reason(s) the subject was not enrolled.

Exclusion codes:

1. Meets all inclusion/exclusion criteria but does not wish to participate
2. Is less than 18 years old
3. Has no ischemic symptoms
4. Onset of symptoms greater than 6 hours prior to enrollment
5. Is not expected to undergo PCI
6. ECG was not indicative of acute STEMI
7. Subject not able to provide informed consent
8. Unable to be followed for 3 months for evaluation
9. Evidence of active infection

Source Data Form

HEAT
Hypothetical Example of **A** Trial

Subject Name: _____ Study Number: __ __ __ - __ __ __

Time study drug dose started: __ __ / __ __ __ / __ __ __ __ (day / month / year) __ __ : __ __ (00:00 to 23:59)

Timepoint	Study Test or Procedure
Before start of study drug: __ __ / __ __ __ / __ __ __ __ (day / month / year) __ __ : __ __ (00:00 to 23:59)	☐ PK/PD samples ☐ CBC/Chemistry panel ☐ 12-lead ECG ☐ Urine specific gravity: _____ BP / Pulse Lying: _____ / _____ _____ Sitting: _____ / _____ _____ Standing: _____ / _____ _____ Pain score (1–10): _____
12 hours after start of study drug: __ __ / __ __ __ / __ __ __ __ (day / month / year) __ __ : __ __ (00:00 to 23:59)	☐ PK/PD samples ☐ CBC/Chemistry panel ☐ 12-lead ECG ☐ Urine specific gravity: _____ BP / Pulse Lying: _____ / _____ _____ Sitting: _____ / _____ _____ Standing: _____ / _____ _____ Pain score (1–10): _____
24 hours after start of study drug: __ __ / __ __ __ / __ __ __ __ (day / month / year) __ __ : __ __ (00:00 to 23:59)	☐ PK/PD samples ☐ CBC/Chemistry panel ☐ 12-lead ECG ☐ Urine specific gravity: _____ BP / Pulse Lying: _____ / _____ _____ Sitting: _____ / _____ _____ Standing: _____ / _____ _____ Pain score (1–10): _____

_____
Signature of person recording data

__ __ / __ __ __ / __ __ __ __ (day / month / year)
Date

For questions regarding the HEAT protocol call 123-555-6789 or page 123-555-0000

Visit Tracking Log

HEAT
Hypothetical Example of A Trial

- Record scheduled date in pencil; record in ink when visit has been completed.
- Contact subject a week before scheduled visit as a reminder.
- Schedule ECG and blood samples for morning of visit.

Enrollment Visit 1 Week 0	Subj. Initials	Study Number	Randomization Visit 2 Week 1	Visit 3 Week 2	Visit 4 Week 4	Visit 5 Week 6	Visit 6 Week 8	Study Completion Visit 7 Week 12
08/JAN/2009	XYZ	001	15/JAN/2009	22/JAN/2009	05/FEB/2009	19/FEB/2009	05/MAR/2009	
17/JAN/2009	ABC	002	24/JAN/2009	31/JAN/2009	14/FEB/2009	28/FEB/2009		
02/FEB/2009	CDE	003	09/FEB/2009	16/FEB/2009	23/FEB/2009			
21/FEB/2009	PDQ	004	28/FEB/2009	07/MAR/2009				

Appendix B

Subject Visit Calculator

Use this visit calculator to project future study visits.

1. Enter the actual date and time of the Enrollment/Randomization Visit. Future study visits will be projected from the Enrollment/Randomization date and time.
2. Record the actual dates the subject is seen for study visits in the "Actual Date/Time" column.
3. If a randomization date or time is entered in error, enter the correct date or time and press enter. The field will automatically be populated with the new information.
4. For each subject, save the calculator as a separate file. Maintain the spreadsheet electronically or print out once the projected dates are populated.

Day 0 Enrollment/Randomization	Actual Date/Time 9/1/2009 12:00 PM	
Visits	**Projected Date/Time**	**Actual Date/Time**
Day 1	**Between** 9/2/2009 10:00AM **and** 9/2/2009 2:00PM	
Day 2	**Between** 9/3/2009 10:00AM **and** 9/3/2009 2:00PM	
Day 3	**Between** 9/4/2009 10:00AM **and** 9/4/2009 2:00PM	
Day 4	**Between** 9/5/2009 10:00AM **and** 9/5/2009 2:00PM	
Day 5	**Between** 9/6/2009 10:00AM **and** 9/6/2009 2:00PM	
Day 6	**Between** 9/7/2009 10:00AM **and** 9/7/2009 2:00PM	

HEAT
Hypothetical Example of A Trial

Protocol-Study #: ___ ___ ___ – ___ ___ ___ (protocol number / site number) Subject's Initials: ___ ___ ___ (first middle last)

Subject Contact Information

Subject Contact Information (please print)

Subject Identification

Subject name: _____ (Last), _____ (First) _____ (Middle)

Resident identification number: _____ **Medical record number:** _____

Primary home address: _____

Primary home phone number: _____ → Best time to call: _____ ☐ AM ☐ PM

Business phone number: _____ → Best time to call: ☐ AM ☐ PM

E-mail address: _____

Spouse or significant other: _____ (Last), _____ (First) _____ (Middle)

Spouse/significant other business name: _____

Spouse/significant other business phone number: _____

E-mail address: _____

Secondary Residence (vacation home, etc.)

Mailing address: _____

Phone number: _____ → Best time to call: _____ ☐ AM ☐ PM

Alternative Contacts *(please list two relatives, friends or neighbors **not living with** subject)*

1 **Name:** _____ (Last), _____ (First) _____ (Middle)

Relationship to subject: _____

Mailing address: _____

Phone number: _____ → Best time to call: _____ ☐ AM ☐ PM

E-mail address: _____

2 **Name:** _____ (Last), _____ (First) _____ (Middle)

Relationship to subject: _____

Mailing address: _____

Phone number: _____ → Best time to call: _____ ☐ AM ☐ PM

E-mail address: _____

Local/Referring Physician or Primary Care Physician/General Practitioner

Name: _____ (Last), _____ (First) _____ (Middle)

Mailing address: _____

Physician's office phone number: _____ **Office fax number:** _____

Contains confidential subject information. Do NOT fax or send this page with subject's case report form.

HEAT
Hypothetical Example of A Trial

Sample Study Close-out Checklist

Site# __ __ __

Review your study file and confirm that all items are present.

1. Protocol/Amendment(s)
   - ❑ Protocol and Signature Page (Investigator's Agreement) dated May 30, 2008
   - ❑ Protocol amendment dated February 19, 2009

2. Investigator's Brochure/Safety Alerts/Data Safety Monitoring Board (DSMB)
   - ❑ Investigator's Brochure dated February 19, 2008
   - ❑ Safety Alert #1004 dated January 19, 2009
   - ❑ DSMB Letter dated May 26, 2009

3. IRB Approved Consent Form(s) and Expiration Date (if applicable)
   - ❑ Version_____dated___/___/___ expiration ___/___/___ or ❑ NA
   - ❑ Version_____dated___/___/___ expiration ___/___/___ or ❑ NA

4. IRB Approval Letter(s)
   - ❑ Protocol version dated May 30, 2008
   - ❑ Protocol amendment dated February 19, 2009
   - ❑ Consent form dated May 30, 2008
   - ❑ Consent form dated February 19, 2009
   - ❑ Recruitment advertisements dated May 30, 2008
   - ❑ Office advertisement posters dated May 30, 2008
   - ❑ Patient newsletter dated December 15, 2008

5. IRB Communications
   - ❑ IRB membership roster(s)
   - ❑ Annual IRB progress report
   - ❑ IRB notification of serious and drug related events; protocol violations/deviations
   - ❑ Other: _____
   - ❑ Final report submitted to IRB: ___/___/___ to sponsor: ___/___/___

6. Form FDA 1572 / Site Signature and Delegation Log
   - ❑ Form FDA 1572 signed ___/___/___
   - ❑ Revised Form FDA 1572 signed ___/___/___
   - ❑ Site Signature and Delegation Log

7. Annual Financial Disclosure and Conflict of Interest Forms
   - ❑ Principal Investigator
   - ❑ Sub-Investigator or ❑ NA

8. Curriculum Vitae (CV) and Medical License
   - ❑ Principal Investigator license expiration date ___/___/___
   - ❑ Sub-Investigator or ❑ NA license expiration date ___/___/___

9. Laboratory Certifications
   - ❑ Clinical Laboratory Improvement Amendment (CLIA) expiration date:___/___/___
   - ❑ College of American Pathologist (CAP) expiration date:___/___/___ or ❑ NA
   - ❑ Laboratory normal ranges

10. Study Drug Records
    - ❑ Study Drug Packing Invoice
    - ❑ Dispensing Logs
    - ❑ Study Drug return forms

11. Training for Key Site Personnel
    - ❑ Human subject protection training
    - ❑ Investigator Meeting attendance certificates
    - ❑ Electronic data capture training

12. Study Logs
    - ❑ Screening Logs
    - ❑ Confidential Master Subject Logs
    - ❑ Site Visit Log(s)

13. ❑ Study Correspondence

Planned storage area for subject data records: _____

Planned storage area for subject consent forms: _____

Planned storage area for financial contracts: _____

Planned storage area for study files: _____

_____ _____

Print Name of Principal Investigator | Signature of Principal Investigator

Date:_____

HEAT
Hypothetical Example of A Trial

Confidential Master Subject Log

Investigator Name: _____ Site #: _ _ _ Page _ of _

ICH Guidelines require keeping a master subject identification log to serve as proof that the site's subjects are real people. This list is confidential and will not be forwarded to the coordinating center at any time.

- Complete all fields for each subject randomized.
- Subject ID Number: Record a unique identifier for each subject. Appropriate numbers may include a medical record number, social security number, or driver's license number (including the state of issue).

Date Consent Signed	Subject Study Number	Subject Initials	Subject ID Number (Medical Record, SS, Driver's License)	Subject Phone Number
	_ _ _ - _ _ _ _ site# subject#	___ ___ ___		
	_ _ _ - _ _ _ _ site# subject#	___ ___ ___		
	_ _ _ - _ _ _ _ site# subject#	___ ___ ___		
	_ _ _ - _ _ _ _ site# subject#	___ ___ ___		
	_ _ _ - _ _ _ _ site# subject#	___ ___ ___		

Appendix B

HEAT
Hypothetical Example of A Trial

HEAT Site Visit Log

SiteNumber: _ _ _

Date(s) of Visit	Visit Type	Name and Role (please print)	Signature	Site Personnel Signature
	❑ Initiation ❑ Periodic ❑ Close-Out ❑ Other (specify): _____			
	❑ Initiation ❑ Periodic ❑ Close-Out ❑ Other (specify): _____			
	❑ Initiation ❑ Periodic ❑ Close-Out ❑ Other (specify): _____			
	❑ Initiation ❑ Periodic ❑ Close-Out ❑ Other (specify): _____			

Appendix C

CONSENT FORM

For A Research Study

A Long Term, Multicenter Study to Evaluate the Tolerability of Drug IOI in Patients with Type 1 Diabetes Mellitus

You are being asked to be in a research study. The study doctor will explain the study to you. The information in this consent form is provided so that you can read about the study and understand what you need to do if you decide to be in the study. You are free to join the study or not. Please take your time to make your decision about taking part. The study doctor and staff will answer any questions you have about the study. You may also want to discuss it with your family and friends, and your health care team. If you decide to be in the study, you can change your mind later and stop participating even if you agreed earlier. If you decide not to join, all the health care services you receive at this clinic for your diabetes will continue.

You are being asked to be in the study because you have Type 1 Diabetes Mellitus.

Why is this study being done?

XYZ Pharmaceutical Company, Inc., and AAA Diabetes Center are doing a study on type 1 diabetes mellitus. Type 1 diabetes mellitus often occurs in children and young adults, and is sometimes called “juvenile diabetes.” In type 1 diabetes, the body does not make insulin, which is necessary for the body to use sugar. Sugar is the basic fuel for the cells in the body, and insulin takes the sugar from the blood into the cells. People with type 1 diabetes must take shots of insulin every day.

Some people who take insulin for their diabetes are not able to keep a steady amount of sugar in their blood. Instead they might have times when their blood sugar is very high, and other times when it is very low. Drug IOI (Instead Of Insulin) is a new drug made by XYZ Pharmaceutical Company, Inc. The XYZ Pharmaceutical Company and the doctors at AAA Diabetes Center would like to know if Drug IOI is safe and if it works well in keeping a steady amount of sugar in the blood.

This study has been approved by the U.S. Food and Drug Administration (FDA), by the AAA Diabetes Center, and at each research review committee (called Institutional Review Boards or IRBs) of the hospitals in the study.

How many people will be in this study?

Approximately 300 people at twenty different hospitals in the United States will be in this study.

To be in the study, people must:

- be between the ages of 16 and 75 years
- have stable control with insulin for their type 1 diabetes mellitus
- not have any long term or current diseases other than diabetes
- not be addicted to alcohol or drugs
- not have been in another research study and taken any other investigational drug during the 90 days before this study
- never have taken Drug IOI before.

What will happen if I decide to be in this study?

Before you begin the study…

The doctor will do a physical examination and ask you questions about your health. Blood tests will be drawn and you will need to give a urine sample. We will measure your blood pressure and heart rate and do an electrocardiogram (also called an ECG which is a record of the electrical impulses of your heart). If you are a female and able to have children, you will have a blood test to be sure you are not pregnant. You will be required to use contraceptives during the entire time you are in the study (approximately 1 year but it may be longer).

Once the study begins…

STUDY DRUG

You will take Drug IOI four (4) times a day. You will need to inject the dose of Drug IOI under the skin on your abdomen.

Study participants will need to take Drug IOI for 52 weeks (one year) after the last person begins the study. Since we think it will take about 3 months to get all 300 people in the study, you might need to take Drug IOI for 15 months or more if you are one of the first people in the study. The study doctor can let you know how many people are in the study before you begin.

CLINIC VISITS

You will have 9 scheduled visits to see the study doctor in the clinic during the time you are in the study. If you have problems, you may contact the study doctor and come in between the scheduled visits. It is also possible that the study staff will ask you to come in for an extra visit if they believe it is necessary.

At each visit, you will have a brief physical examination and a blood test. The amount of blood taken on each visit will equal about 2 teaspoons. Before the blood tests on visit #1, 5, and 9, you should not have anything to eat or drink for 9 hours before your blood is taken.

On visits #1, 5, and 9 you will also have an ECG done. Women who are able to have children and are using contraceptives will have a blood pregnancy test done at each visit.

STUDY DRUG GROUPS

At visit #5, the results of your hemoglobin A1c (a blood test that shows how stable your blood sugar levels have been), will determine if you will go into a sub-group of people who may be assigned to a higher dose of Drug IOI. This is done to see if the higher dose of Drug IOI has a better effect and if it has any side effects.

Some people will not be eligible to go into the sub-group. These people will continue to take Drug IOI at the original dose until the end of the study. We will not know if you can go into the sub-group until we have the results of your hemoglobin A1c drawn at visit #5.

This decision of who gets this higher dose of Drug IOI and who continues on with the original dose is random, like a toss of a coin. You have a fifty-fifty (50%) chance of receiving the higher dose, and the same chance for continuing on with the original dose. Neither you nor your study doctor will know which dose you are receiving. Information about which dose you are on will be known only to a few people at XYZ Pharmaceutical Company. If for some medical reason we need to find out, they will be able to tell us. This is the best method we have for testing a drug without being influenced by what we think or hope might happen.

STUDY EXTENSION

At the end of the 52 weeks (visit #9), you may be asked to participate in an extension of the study. If you are asked and you agree to participate in the extension, you will need to sign a new consent form for the extension.

OTHER HEALTH CARE NEEDS

You should continue to see your regular doctors for your other health care needs. We will give you a card to carry in your wallet that tells about the study you are in and who to call if your other health care providers have questions.

At the end of the study…

At the end of the study, you will have a final visit with the study doctor. At this visit you will have a physical examination, blood tests, urine test, and ECG.

Once the study is over, you will stop taking Drug IOI and start taking insulin as you did before the study.

Can I stop being in the study?

Yes, you can stop being in the study at any time. It is important to tell the study doctor that you are thinking about stopping so that you can safely be put back on your insulin.

The study doctor may stop you from participating if at any time he believes it is in your best interest. The study doctor will stop you from being in the study if you do not take Drug IOI as required for the study, if you are not following other study rules, or if the study is stopped by the XYZ Pharmaceutical Company for any reason.

What side effects or risks can I expect from being in this study?

Since Drug IOI is a new drug and has not been taken by a large number of people, we do not know all of its side effects. We will watch you carefully for any side effects while you are taking Drug IOI. In a previous study, 1 out of 10 people who took Drug IOI had nausea and flushing the first few times they took it. A few people had vomiting and diarrhea. All of these side effects had disappeared by the third week. If you have side effects you should tell your study doctor right away. The study doctor may decide to give you some treatment to help reduce your side effects.

You may feel a slight sting or "pinch" when your blood is drawn at the visits. You may also get a small bruise where the needle went in.

You may have slight swelling or tenderness in your abdomen where you inject Drug IOI.

Are there benefits from being in this study?

You will receive Drug IOI for free during the study. You will not pay for your visits to the study doctor or for the blood tests and ECGs that are done for this study. Being in this study may or may not make your diabetes better. While we hope that Drug IOI will be better than insulin in type I diabetes, there is no proof of this yet. The information from this study may help doctors learn more about how the body uses drugs like IOI and insulin.

What other choices do I have if I do not take part in this study?

If you do not want to be in this study, you can continue taking insulin for your diabetes.

Will my medical information be kept private?

The information we get from you will be kept private to the extent allowed by law. To protect your privacy, we will keep your records under a code number rather than by your name. We will keep your records in a locked file and only study staff, including people from XYZ Pharmaceutical Company and the Food and Drug Administration, will be allowed to look at them. Your name and other facts that might identify you will not appear when we present this study or publish the results.

What are the costs of taking part in this study?

The only cost to you for being in the study is the time you must spend and what it costs for you to get to the clinic for your visits. Each visit should take approximately 1 hour or less of your time.

You will be given $100 for being in this study. This is to help pay for your time and the cost of coming to the clinic. You will receive this even if you need to stop taking Drug IOI before the 52 weeks are up.

What happens if I am injured because I am in this study?

It is important to tell your study doctor, Dr. Doe, right away if you think you have been injured because of being in this study. You can tell Dr. Doe in person or by calling her at 765-678-1234. You will get treatment for a study-related injury at no charge to you. It is your responsibility to pay the cost of other medical care that is not related to this specific injury.

What are my rights if I am in the study?

Taking part in this study is your choice. You may choose to be in the study or not. If you decide to be in the study, you can change your mind and leave the study at any time. Leaving the study will not affect your medical care.

We will tell you about new information or changes in the study that may affect your health or your willingness to be in the study.

In case of injury resulting from being in this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to Dr. Doe about any questions or concerns you have about this study. You may contact Dr. Doe at 765-678-1234.

For questions about your rights while being in this study, you may call the IRB at AAA Diabetes Center at 765-876-4321. The IRB has reviewed and approved this study and will be able to answer your questions about your rights as a participant in a research study.

Voluntary Consent to Participate

I have read this consent form or it has been read and explained to me. All of my questions have been answered at this time. I understand that my signature below shows my agreement to be in the study. I realize that I can leave the study at any time if I change my mind.

Signature of Participant	Date of Signature
Signature of Person Obtaining Consent	Date of Signature

U.S. Code of Federal Regulations

Consent Form Checklist

Make sure all required elements and all applicable additional elements are included in the consent form.

21 CFR 50.25

Required Elements

1. A statement that the study involves research

   Explanation of the purpose of the study

   Expected duration of the study; expected duration of the subject's participation

   Description of the procedures the subject will undergo in the study

   Identification of any procedures that are experimental
2. Description of reasonably foreseeable risks or discomforts
3. Description of benefits
4. Explanation of alternative procedures or courses of treatment if the person chooses not to participate
5. Description of confidentiality of records; statement that the FDA and the sponsor may view and inspect subject records
6. Explanation of compensation and medical treatment for injury occurring during the study
7. The name of persons to contact for answers to study-related questions and research-related injury
8. Statement that participation is voluntary with no penalty or loss of benefits for refusal to participate; statement that subject can stop participating at any time without penalty or loss of benefits

Additional Elements

1. Statement that unforeseeable risks to the subject, embryo, or fetus may exist
2. Circumstances in which the subject's participation may be terminated by the investigator
3. Additional costs to the subject resulting from study participation
4. Consequences of and procedures for withdrawal (e.g., tapering drug dose)
5. Statement that subjects will be informed about significant new findings that might affect their willingness to continue participation
6. Approximate number of subjects participating in the study

ICH Guidelines

Consent Form Checklist

Make sure all items are included in the consent

form to comply with ICH guidelines

ICH Section 4.8.10

1. The study involves research
2. The purpose of the study
3. Trial treatments and the probability for random assignment to each treatment group
4. Trial procedures, including all invasive procedures
5. Subject's responsibilities
6. Aspects of the trial that are experimental
7. Reasonably foreseeable risks or inconveniences
8. Reasonably foreseeable benefits (when there is no intended benefit, this should be stated)
9. Alternative treatments or course of therapy
10. Compensation and treatment in the event of study-related injury
11. Payment to subject for participation in the study
12. Anticipated expenses to subject because of study participation
13. Participation is voluntary and the subject may refuse to participate or may withdraw consent at any time without penalty or loss of benefits
14. Study personnel, including monitors (clinical research associates), auditors, IRB members, and regulatory authorities, will have access to the subject's medical records for data verification without violating confidentiality; the signed written consent form provides authorization for this access
15. Records identifying the subject by name will be kept confidential; if results are published, the subject's identity will remain confidential
16. Information relevant to continued study participation will be provided to the subject in a timely manner
17. Name and number of person the subject can contact for information regarding the rights of study subjects and trial-related injury
18. Circumstances in which the subject may be prematurely withdrawn from the study
19. Expected duration of the subject's participation
20. Approximate numbers of subjects involved in the study

Appendix D

Form FDA 1572 – FDA has OMB approval to use this form until 8/31/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES 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: May 31, 2009. *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.

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). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

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:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-143)
Central Document Room
5901-B Ammendale Road
Beltsville, MD 207052-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

"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.

Health Canada / Santé Canada

QUALIFIED INVESTIGATOR UNDERTAKING
Natural Health Products Directorate

An undertaking must be completed by the qualified investigator responsible for the conduct of the clinical trial at the site specified below. The completed undertaking must be retained by the clinical trial sponsor for a period of 25 years.

Part 1: Clinical Trial Protocol Information

Please check one of the following:

☐ **Clinical Trial Application (CTA)**

☐ **Clinical Trial Application Amendment (CTA-A)**

☐ **Clinical Trial Notification**

Protocol Title

Protocol **#** (if known)

Part 2: Natural Health Product (NHP) / Sponsor Information

A. NHP Information

Brand Name / Product Code:

Medicinal Ingredient(s):

☐ See Clinical Trial Application and Attestation Form

Submission Number (if known):

B. Sponsor of Clinical Trial

Name of Sponsor (Full Name – No Abbreviations)			
Street / Suite / PO Box			
City / Town	Province / State	Country	Postal / ZIP Code

C. Contact for this Clinical Trial

Contact Name		E-mail	
Company Name (Full Name – No Abbreviations)			
Street / Suite / PO Box			
City / Town	Province / State	Country	Postal / ZIP Code
Telephone No.		Fax No.	

Canada

Part 3: Qualified Investigator Information			
A. Clinical Trial Site			
Name of Site (Full Name – No Abbreviations)			
Street / Suite / PO Box			
City / Town	Province	Postal Code	
B. Qualified Investigator			
Name	Title	Language Preferred ☐ English ☐ French	
Street / Suite / PO Box			
City / Town	Province	Postal Code	
E-mail	Telephone No.	Fax No.	

In respect of the identified clinical trial, I certify, as the qualified investigator for this site that:

1. I am a physician or dentist and a member in good standing of a professional medical or dental association as defined in Part 4 of the *Natural Health Products Regulations*;
2. I will supervise the medical care and medical decisions respecting this clinical trial at this site;
3. I will conduct this clinical trial in accordance with Good Clinical Practices; and
4. I will immediately on discontinuance of the clinical trial by the sponsor, in its entirety or at a clinical trial site, inform both the clinical trial subjects and the Research Ethics Board for this site of the discontinuance, provide them with the reasons for the discontinuance, and advise them in writing of any potential risks to the health of clinical trial subjects or other persons.

Signature of Qualified Investigator	Date					
	YYYY		M		D	

Health Canada Santé Canada

RESEARCH ETHICS BOARD ATTESTATION
Natural Health Products Directorate

An attestation must be completed by the Research Ethics Board that reviewed and approved the clinical trial protocol and informed consent form for this clinical trial at the site below. The completed attestation must be retained by the clinical trial sponsor for a period of 25 years.

Part 1: Clinical Trial Protocol Information			
Please check one of the following: ☐ **Clinical Trial Application (CTA)** ☐ **Clinical Trial Application Amendment (CTA-A)**			
Protocol Title			
Protocol # (if known)			
Part 2: Natural Health Product (NHP) / Sponsor Information			
A. NHP Information			
Brand Name / Product Code:			
Medicinal Ingredient(s): ☐ See Clinical Trial Application and Attestation Form Submission Number (if known):			
B. Sponsor of Clinical Trial			
Name of Sponsor (Full Name – No Abbreviations)			
Street / Suite / PO Box			
City / Town	Province / State	Country	Postal / ZIP Code
C. Contact for this Clinical Trial			
Contact Name	E-mail		
Company Name (Full Name – No Abbreviations)			
Street / Suite / PO Box			
City / Town	Province / State	Country	Postal / ZIP Code
Telephone No.	Fax No.		

Canada

Part 3: Clinical Trial Site Information

A. Clinical Trial Site

Name of Site (Full Name – No Abbreviations)		
Street / Suite / PO Box		
City / Town	Province	Postal Code

B. Qualified Investigator

Name	Title	Language Preferred ☐ English ☐ French
Street / Suite / PO Box		
City / Town	Province	Postal Code

E-mail	Telephone No.	Fax No.

Attach separate sheets (same format) for each Clinical Trial Site.

Number of pages attached:

C. Research Ethics Board Approval	☐ Includes member knowledgeable in complementary or alternative health care (identify member and expertise in the cover letter)

Name of Research Ethics Board			Date of Approval
Street / Suite / PO Box			
City / Town	Province		Postal Code
Name of Research Ethics Board Chair	Telephone No.	Fax No.	Language Preferred ☐ English ☐ French
Title	E-mail		

In respect of the identified clinical trial, I certify, as representative of this Research Ethics Board that:

1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the *Natural Health Products Regulations*;
2. This Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices; and
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Board have been documented in writing.

Name, Title and Signature of Research Ethics Board Representative		Date					
Name:	Title:	YYYY		M		D	
Signature:							

Clinical Trial Process
United States, Canada, and Singapore

	United States	Canada	Singapore
Regulatory Agency	Food and Drug Administration (FDA) www.fda.gov	Health Canada www.hc-sc.gc.ca	Health Sciences Authority (HSA) www.hsa.gov.sg
Clinical Trials Regulations	Code of Federal Regulations (CFR); Good Clinical Practice Consolidated Guideline (ICH GCP Guidelines)	Health Canada Food and Drugs Act and Regulations; Good Clinical Practice Consolidated Guideline (ICH GCP Guidelines)	Medicines (Clinical Trials) Regulations Singapore Guideline for Good Clinical Practice (SGGCP) adapted from the ICH Guideline for Good Clinical Practice
Privacy/Data Protection Regulations or Policy	Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule	Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, Section 3: Privacy and Confidentiality (2005) Canadian Institutes of Health Research (CIHR) Best Practices for Protecting Privacy in Health Research (2005)	Personal Information in Biomedical Research (2007) [*A Report by the Bioethics Advisory Committee*]
Process	Investigational New Drug (IND) application is submitted to the FDA for drugs and biologics; Investigational Device Exemption (IDE) for devices.	Clinical trials application (CTA) is submitted to the Therapeutic Products Directorate (TPD).	Each PI participating in a clinical trial of a medicinal product must obtain a Clinical Trial Certificate (CTC) from the HSA before study initiation. PIs can submit the study for Institutional Review Board approval at the same time the application for a CTC is submitted.
Ethics Committee/IRB Approval	IRB (Institutional Review Board) Approval varies from institution to institution. Central IRBs may be used.	Research Ethics Board (REB) Many community hospitals do not have their own REB therefore central REBs are frequently used. REB Attestation (REBA) form must be signed by the REB chairperson.	Centralised Institutional Review Board/Domain Specific Review Boards (DSRBs) review and approve protocols in designated subspecialty areas.

Clinical Trial Process
United States, Canada, and Singapore

	United States	Canada	Singapore
Regulatory Agency Approval	30-day review period. The FDA only issues disapproval (via a clinical hold) of the IND application rather than approval to begin clinical testing If FDA reviewers identify safety concerns, they will notify the sponsor to issue a "clinical hold." The clinical trial may not be initiated until the issues or concerns that led to a clinical hold are resolved.	30-day review period. If TPD does not issue a non-satisfactory notice (NSN) during the review period, the trial may proceed on the basis of default authorization. Health Canada no objection letter (NOL) is issued to the sponsor. Sponsor will provide copy of NOL to site upon request.	30-day review period. HSA regulatory approval is issued independent of IRB approval. The study can only be initiated after both regulatory and IRB approval is obtained.
Record Retention	At least **2 years following the approval** of a New Drug Application.	All site clinical trial records must be maintained by the site and/or sponsor for 25 years.	At least **2 years after the last approval** of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, or 6 years after the completion of the clinical trial.
Site Inspections	FDA inspectors	Health Canada compliance inspectors	HSA is currently developing a site inspections program.
Special Regulatory Forms	FDA Form 1572 signed by the principal investigator.	Qualified Investigator Undertaking (QIU). Only 1 qualified investigator is allowed per site.	Clinical Trial Certificate for each PI in a trial.

The Office for Human Research Protections (OHRP) in the U.S. Department of Health and Human Services (DHHS) has compiled laws, regulations, and guidelines that govern human research protections for 92 countries. The 2009 edition of this compilation can be found at the Web site: http://www.hhs.gov/ohrp/international/HSPCompilation.pdf

Appendix D

Appendix E

Selected Regulations for Drugs, Biologics, and Devices

21 CFR 11 – Electronic Records; Electronic Signatures

Subpart A – General Provisions

11.1 Scope
11.2 Implementation
11.3 Definitions

Subpart B – Electronic Records

11.10 Controls for closed systems
11.30 Controls for open systems
11.50 Signature manifestations
11.70 Signature/record linking

Subpart C – Electronic Signatures

11.100 General Requirements
11.200 Electronic signature components and controls
11.300 Controls for identification codes/passwords

21 CFR 50 – Protection of Human Subjects

Subpart A – General Provisions

50.1 Scope
50.3 Definitions

Subpart B – Informed Consent of Human Subjects

50.20 General requirements for informed consent
50.23 Exception from general requirements
50.24 Exception from informed consent requirements for emergency research
50.25 Elements of informed consent
50.27 Documentation of informed consent

Subpart D – Additional Safeguards for Children in Clinical Investigations

50.50 IRB duties
50.51 Clinical investigations not involving greater than minimal risk
50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects
50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition
50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children
50.55 Requirements for permission by parents or guardians and for assent by children
50.56 Wards

21 CFR 54 – Financial Disclosure by Clinical Investigators

54.1 Purpose
54.2 Definitions
54.3 Scope
54.4 Certification and disclosure requirements
54.5 Agency evaluation of financial interests
54.6 Recordkeeping and record retention

21 CFR 56 – Institutional Review Boards

Subpart A – General Provisions

56.101 Scope
56.102 Definitions
56.103 Circumstances in which IRB review is required
56.104 Exemptions from IRB requirement
56.105 Waiver of IRB requirement

Subpart B – Organization and Personnel

56.106 Registration
56.107 IRB membership

Subpart C – IRB Functions and Operations

56.108 IRB functions and operations
56.109 IRB review of research
56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research
56.111 Criteria for IRB approval of research
56.112 Review by institution
56.113 Suspension or termination of IRB approval of research
56.114 Cooperative research

Subpart D – Records and Reports

56.115 IRB records

Subpart E – Administrative Actions for Noncompliance

56.120 Lesser administrative actions
56.121 Disqualification of an IRB or an institution
56.122 Public disclosure of information regarding revocation
56.123 Reinstatement of an IRB or an institution
56.124 Actions alternative or additional to disqualification

21 CFR 312 – Investigational New Drug Application

Subpart A – General Provisions

Subpart B – Investigational New Drug Application (IND)

Subpart C – Administrative Actions

Subpart D – Responsibilities of Sponsors and Investigators

21 CFR 312 – Investigational New Drug Application

Subpart D – Responsibilities of Sponsors and Investigators (continued)

312.61 Control of the investigational drug
312.62 Investigator recordkeeping and record retention
312.64 Investigator reports
312.66 Assurance of IRB review
312.68 Inspection of investigator's records and reports
312.69 Handling of controlled substances
312.70 Disqualification of a clinical investigator

21 CFR 600 – 680 Biologics

21 CFR 600 Biological products: general
21 CFR 601 Licensing
21 CFR 610 General biological products standards
21 CFR 680 Additional standards for miscellaneous products

21 CFR 812 – Investigational Device Exemptions

Subpart A – General Provisions

812.1 Scope
812.2 Applicability
812.3 Definitions
812.5 Labeling of investigational devices
812.7 Prohibition of promotion and other practices
812.10 Waivers
812.18 Import and export requirements
812.19 Address for IDE correspondence

Subpart B – Application and Administrative Action

812.20 Application
812.25 Investigational plan
812.27 Report of prior investigations
812.30 FDA action on applications
812.35 Supplemental applications
812.36 Treatment use of an investigational device
812.38 Confidentiality of data and information

Subpart C – Responsibilities of Sponsors

812.40 General responsibilities of sponsors
812.42 FDA and IRB approval
812.43 Selecting investigators and monitors
812.45 Informing investigators
812.46 Monitoring investigations
812.47 Emergency research under 50.24 of this chapter

21 CFR 812 – Investigational Device Exemptions (continued)

Subpart D – IRB Review and Approval

812.60 IRB composition, duties, and functions
812.62 IRB approval
812.64 IRB's continuing review
812.66 Significant risk device determinations

Subpart E – Responsibilities of Investigators

812.100 General responsibilities of investigators
812.110 Specific responsibilities of investigators
812.119 Disqualification of a clinical investigator

Subpart G – Records and Reports

812.140 Records
812.145 Inspections
812.150 Reports

45 CFR 46 – Protection of Human Subjects

Subpart A – Basic HHS Policy for Protection of Human Research Subjects

46.101 To what does this policy apply?
46.102 Definitions
46.103 Assuring compliance with this policy–research conducted or supported by any Federal Department or Agency
46.107 IRB membership
46.108 IRB functions and operations
46.109 IRB review of research
46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research
46.111 Criteria for IRB approval of research
46.112 Review by institution
46.113 Suspension or termination of IRB approval of research
46.114 Cooperative research
46.115 IRB records
46.116 General requirements for informed consent
46.117 Documentation of informed consent
46.118 Applications and proposals lacking definite plans for involvement of human subjects
46.119 Research undertaken without the intention of involving human subjects
46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency
46.122 Use of Federal funds
46.123 Early termination of research support: Evaluation of applications and proposals
46.124 Conditions

45 CFR 46 – Protection of Human Subjects (continued)

Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

46.201 To what do these regulations apply?
46.202 Definitions
46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates
46.204 Research involving pregnant women or fetuses
46.205 Research involving neonates
46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material
46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates

Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

46.301 Applicability
46.302 Purpose
46.303 Definitions
46.304 Composition of Institutional Review Boards where prisoners are involved
46.305 Additional duties of the Institutional Review Boards where prisoners are involved
46.306 Permitted research involving prisoners

Subpart D – Additional Protections for Children Involved as Subjects in Research

46.401 To what do these regulations apply?
46.402 Definitions
46.403 IRB duties
46.404 Research not involving greater than minimal risk
46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
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
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
46.408 Requirements for permission by parents or guardians and for assent by children
46.409 Wards

ICH E6 – Guideline for Good Clinical Practice

For a complete list of guidelines, refer to the ICH Web site.

1. Glossary
2. The Principles of ICH GCP
3. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
   - 3.1 Responsibilities
   - 3.2 Composition, Functions, and Operations
   - 3.3 Procedures
   - 3.4 Records
4. Investigator
   - 4.1 Investigator's Qualifications and Agreement
   - 4.2 Adequate Resources
   - 4.3 Medical Care of Trial Subjects
   - 4.4 Communication with IRB/IEC
   - 4.5 Compliance with Protocol
   - 4.6 Investigational Product(s)
   - 4.7 Randomization Procedures and Unblinding
   - 4.8 Informed Consent of Trial Subjects
   - 4.9 Records and Reports
   - 4.10 Progress Reports
   - 4.11 Safety Reporting
   - 4.12 Premature Termination or Suspension of a Trial
   - 4.13 Final Reports by Investigator/Institution
5. Sponsor
6. Clinical Trial Protocol and Protocol Amendment(s)
7. Investigator's Brochure
8. Essential Documents for the Conduct of a Clinical Trial

References and Resources

Documents Regarding Ethical Framework for Clinical Trials

The Belmont Report
http://ohsr.od.nih.gov/guidelines/belmont.html

The Declaration of Helsinki (2008 version)
http://www.wma.net/en/30publications/10policies/b3/index.html

The Nuremberg Code
http://ohsr.od.nih.gov/guidelines/nuremberg.html

US Regulations and Guidance Documents

US Food and Drug Administration
http://www.fda.gov

Code of Federal Regulations Title 21 (FDA)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

Code of Federal Regulations Title 45 (NIH)
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

Federal Register
http://www.gpoaccess.gov/fr/index.html

FDA Information Sheet Guidances — Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors
http://www.fda.gov/oc/ohrt/irbs/default.htm

Clinical Trials Registration
http://clinicaltrials.gov/

Office for Human Research Protections (OHRP)
http://www.hhs.gov/ohrp/

ICH International Conference on Harmonisation

ICH home page
http://www.ich.org/cache/compo/276-254-1.html

Guidance for Industry. E6 Good Clinical Practice Consolidated Guidance
http://www.fda.gov/downloads/regulatoryinformation/guidances/UCM129515.pdf

Informed Consent

National Cancer Institute (NCI), US National Institutes of Health (NIH), "Simplification of Informed Consent Documents." http://www.cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/.

Education Requirements for Human Subjects Protection

Frequently asked Questions for the Requirement for Education on the Protection of Human Subjects, NIH, Office of Extramural Research
http://www.grants.nih.gov/grants/policy/hs_educ_faq.htm

NIH Required Education in the Protection of Human Research Participants Policy
http://www.grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html

HIPAA

Information regarding the Health Insurance Portability and Accountability Act
http://www.hhs.gov/ocr/privacy/index.html

MedWatch

The FDA Safety Information and Adverse Event Reporting Program
http://www.fda.gov/medwatch/

Writing and Language

Plain Language Home page
http://www.plainlanguage.gov/index.cfm

Training program
http://plainlanguage.nih.gov/CBTs/PlainLanguage/default.asp

SMOG: Simple Measure of Gobbledygook
http://www.harrymclaughlin.com/SMOG.htm

ARGH: Biomedical Acronym Resolver
http://invention.swmed.edu/argh

Protocol Design Resources

Information Sheets/Forms
National Institutes of Health, Office of Human Subjects Research
http://ohsr.od.nih.gov/info/info.html

Cancer Therapy Evaluation Program (CTEP), National Cancer Institute
http://ctep.cancer.gov/protocolDevelopment/default.htm

Training and Educational Opportunities

Cancer Therapy Evaluation Program (CTEP), National Cancer Institute, Investigator's Handbook
http://ctep.cancer.gov/investigatorResources/default.htm#investigators_handbook

Collaborative Institutional Training Initiative (CITI)
http://www.citiprogram.org

Clinical Trials Networks Best Practices
https://www.ctnbestpractices.org

Association for Clinical Research Professionals (ACRP)
http://www.acrpnet.org

Society for Clinical Research Associates (SoCRA)
http://www.socra.org

Drug Information Association (DIA)
http://www.diahome.org

Miscellaneous

Concomitant medications
http://www.pdrhealth.com/drugs/drugs-index.aspx
http://clinicalpharmacology-ip.com/

National Guideline Clearinghouse A public resource for evidence-based clinical practice guidelines
http://www.guideline.gov/

Dry ice vendors by zip code
http://www.dryiceinfo.com/

Epilogue

A great deal has changed in the 10 years since the publication of the first edition of *Lessons from a Horse Named Jim*, and there have been even more dramatic changes since the authors first started in clinical research, more than 20 years ago.

In 1990, modern communications technology was just beginning to be used to support our research. Fax machines were being installed in offices for the first time. Cellular telephones were available, but were cumbersome and expensive and by no means pocket-sized – we could still find payphones on many corners to respond to urgent pages. Use of e-mail was mostly confined to a small handful of "early adopters" and electronic data capture was in its infancy.

In 1990, consent forms were just a few pages long, the Health Insurance Portability and Accountability Act (HIPAA) did not yet exist, and sites were allowed to begin recruiting patients even before a site contract was executed. By way of contrast, in 2009, fewer than 50% of the sites in the United States are ready to enroll subjects within 5 months of a protocol and contract being sent to the participating investigator. Between 15% and 20% of sites that are ultimately approved to enroll subjects in trials never enroll a single one.

A decade ago we were all worried about what would happen to our databases and computers when Y2K arrived; fortunately, it became just another New Year's Eve.

The list of countries around the world that participate in clinical trials has changed considerably, as has the distribution of participating subjects. In 1990, a trial of 41,000 subjects with acute myocardial infarction, conducted in 13 countries, was finished in less than 24 months' time. In 2009, the typical large outcomes trials of 10,000–20,000 subjects requires 40 or more participating countries and more than 800 participating sites, and frequently takes more than 2–3 years to complete.

More recently, both India and China have seen tremendous growth in clinical trials activity. There is currently great excitement among clinical research organizations (CROs) and sponsor outsourcing departments over the possibilities of high subject enrollment and very low research costs offered by these nations. Unfortunately, both countries have been beset by issues relating to data quality as well as

concerns about the process of informed consent. There are, however, tremendous opportunities in these regions and it is critically important that efforts are focused on developing collaborations with regulatory agencies, sponsors, and academic institutions to assure the successful growth of a high-quality, ethically and scientifically sound clinical research enterprise.

As you read through this edition of *Lessons from a Horse Named Jim* (and as you continue participating in clinical research over the next decade), we'd like you to consider the following:

- *The patient is at the center of all research*. Think of what you can do to encourage your patient population to be knowledgeable about medical research and comfortable with participating in clinical trials.
- *Stay focused on the goals of clinical research*. As a local investigator or clinical research coordinator, it is easy to become overwhelmed with the administrative burden of research and lose sight of the ultimate goal. You need to critically evaluate what is being asked of your site by a sponsor and provide clear feedback when resources are being used unnecessarily.
- *Carefully evaluate study feasibility*. You should evaluate all new trial opportunities in a formal, systematic fashion and decline to participate in ones that do not fit your practice.
- *Carefully evaluate your own performance*. You must actively evaluate your own performance regarding enrollment, data quality, and protocol compliance; do not rely on the sponsor or the monitor to do this for you.
- *Work with and learn from others*. Collaborate with other sites to develop formal and informal networks of sites; use these networks to share lessons learned as well as discuss solutions for challenges in managing research.
- *Set high expectations for others*. You should expect that sponsors, academic research organizations, and contract research organizations will provide skilled and clinically knowledgeable staff to work with you at the site.
- *Set high expectations for your own site*. You should commit to providing clinically knowledgeable study staff who are carefully trained in human subjects protection and good clinical practice.

In reflecting upon the previous decades and thinking about the challenges each of us faces in performing high-quality research, it is easy to lose sight of what we as individuals can do to improve the conduct of clinical research and help deliver lifesaving (or life-changing) therapies to our patients. We hope that this edition of *A Horse*

Named Jim will prove a valuable resource to all persons – physicians, nurses, research coordinators, and support staff – who contribute to the difficult but vital, and, we hope, ultimately rewarding effort of advancing medical knowledge and improving the lives of patients around the world.

Lisa G. Berdan PA, MHS
Global Cardiovascular Megatrials
Duke Clinical Research Institute
Durham, North Carolina, USA

Glossary

Academic Research Organization (ARO) An academic organization that sponsors a trial or is contracted by the sponsor to perform one or more of a sponsor's trial-related activities, including but not limited to protocol development and design, recruitment of investigators, study management and coordination, monitoring, data management, and statistical analysis. An ARO may be affiliated with a university or other academic institution and typically uses academic faculty and clinicians to provide clinical trial leadership.

Adverse Drug Reaction (ADR) A response to an *investigational drug* that is noxious and unintended and that occurs at any dose. A response to a *marketed drug* that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function. Adverse drug reactions can be *expected* or *unexpected*.

Adverse Event (AE) Any unfavorable change that occurs during or after treatment with a pharmaceutical product; the change is not necessarily caused by the pharmaceutical product. Includes physical signs and symptoms, abnormal laboratory findings, changes in vital signs, a new condition or illness, or the worsening of a condition or illness that was present before administration of the product. Also called *adverse experience*.

Amendment See *Protocol Amendment.*

Assent A child's agreement to participate in clinical research. Assent may be required from children who are of adequate age and emotional maturity to understand the concept of the study even when not able to grasp all the details of the study.

Assurance of Compliance A legally binding written document that commits a public or private institution to comply with applicable federal minimum standards for the protection of human subjects in research. Under Department of Health and Human Services (DHHS) regulations protecting human research subjects, every institution engaged in research involving human subjects that is funded or conducted by DHHS must obtain an Assurance of Compliance

approved by the Office for Human Research Protections (OHRP). This Assurance of Compliance, when granted, is called a **Federalwide Assurance (FWA)**.

Audit An independent and systematic review of study data and associated records, 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 and is in compliance with the protocol, standard operating procedures, Good Clinical Practice guidelines, and applicable regulations. Sponsors may conduct internal audits, audits of academic research organizations/ contract research organizations designated to perform sponsor responsibilities, and audits of investigative sites participating in a clinical trial. Audits may also be performed to review manufacturing practices, laboratory processes, and storage facilities.

Audit Trail Documentation of all steps that occur between the collection of study data and the data's final disposition in the study database. The audit trail allows auditors to identify the original source of the data and follow the history of any changes made to original documentation.

Belmont Report Report issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979. The Belmont Report identifies basic ethical principles for the conduct of clinical research: respect for persons, beneficence, and justice.

Benefit A valued, favorable, or desired outcome.

Beneficence One of the three ethical principles described in *The Belmont Report*. Beneficence means to do no harm; to maximize possible benefits and minimize possible harms.

Biologic Product A virus, toxin, antitoxin, vaccine, therapeutic serum, blood, blood component, or allergenic product intended for the prevention, treatment, or cure of a disease or condition, including immunoglobulins, cytokines, and other biotechnology-derived products.

Blinding A procedure in which one or more parties in a clinical trial are kept unaware of the treatment assignments to minimize the potential for bias. *Single blinding* usually refers to subjects being unaware of the treatment assignment, while *double blinding* usually refers to both subjects and investigators (and other study personnel) being unaware of the treatment assignments. In case of emergencies that require knowledge of the treatment assignment, mechanisms

exist to *unblind* the code; this is commonly called "*breaking the blind*." An "open" or "open-label" study is one in which there is no blinding of the treatment assignment to either the subject or the study staff.

Case Report Form (CRF) A printed or electronic document used to record protocol-required information collected for each subject in the study.

Causality Assessment A determination of whether a reasonable possibility exists that an adverse event was caused by or related to the use of an investigational product. Examples of categories for causality include: 1) *not a reasonable possibility* – it is unlikely the adverse event was caused by the investigational product, and 2) *a reasonable possibility*–the adverse event may have been caused by the investigational product. This categorization is sometimes expanded to include the following attributions: 1) unrelated, 2) remotely related, 3) possibly related, 4) probably related, and 5) definitely related.

Children (in clinical research) Individuals who are not of legal age to give consent for participation in a clinical research study. Children who are considered of adequate age and emotional maturity may be required to give assent to study participation. Specific legal age is determined under the applicable laws in the jurisdiction where the research is being conducted.

Clinical Research Coordinator (CRC) The person at the study site who is typically responsible for the day-to-day conduct of study activities, including completing case report forms, maintaining study files, assisting the investigator, administering study drug, and communicating with the sponsor. Also called *trial coordinator, study coordinator, research coordinator, research nurse*, and *protocol nurse*.

Clinical Trial Systematic study, often with a component of randomization and conducted in human subjects, that compares an experimental treatment against a standard therapy, no treatment, and/or a placebo.

Code of Federal Regulations (CFR) An annually revised codification of the general and permanent rules established by the U.S. Government and published in the Federal Register. The code is divided into 50 titles that represent broad areas subject to federal regulations. Title 21 of the CFR includes most of the regulations affecting the discovery, development, approval, and marketing of drugs, biologics, and devices.

Coding Assigning data such as adverse events, medical terms, and medications to categories, allowing them to be grouped and

retrieved for analysis. Common coding dictionaries include MedDRA, COSTART, and WHOART.

Compliance Adherence to protocol requirements, standards of Good Clinical Practice (GCP), and applicable regulations.

Confidentiality Prevention of disclosure of information to other than authorized individuals; e.g., a sponsor's propriety information or a subject's identity and protected health information.

Contract Research Organization (CRO) An organization contracted by the sponsor to perform one or more of a sponsor's trial-related activities, including but not limited to protocol development and design, recruitment of investigators, study management and coordination, monitoring, data management, and statistical analysis. CROs differ from academic research organizations (AROs) in that they are typically for-profit companies, and are not affiliated with a university or other academic institution.

Consent Form See *Informed Consent*.

Control Group In a clinical trial, a group of subjects receiving either standard treatment, no treatment, or placebo, who are then compared with a group of subjects receiving the investigational treatment.

Curriculum Vitae (CV) A summary of an individual education, training, and experience (similar to a résumé).

Data and Safety Monitoring Board or Committee (DSMB or DSMC) An independent committee of clinicians, statisticians, ethicists, and other specialists who assess the progress of a trial, its safety, and/or its efficacy at specified intervals. The committee can make recommendations that a study be continued, modified, or stopped based on the data reviewed.

Data Forms Forms used to record subject data from original source documents. Includes but is not limited to case report forms, enrollment forms, serious adverse event forms, and follow-up forms.

Declaration of Helsinki Recommendations adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, guiding physicians in biomedical research involving human subjects. The declaration sets forth requirements for the ethical treatment of subjects and volunteers in research on human subjects. It contains provisions for obtaining informed consent and stresses the overriding importance of research subjects as individuals whose needs take precedence over needs of science and society. The basic thrust of the Declaration of Helsinki is incorporated in the U.S. Code of Federal Regulations

(21 CFR 312). The Declaration of Helsinki has been revised six times since it was adopted in 1964, most recently in 2008.

Device An instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent or other similar or related article, including any component, part or accessory, which is intended for use in the diagnosis, cure, treatment, or prevention of disease. A device does not achieve its intended purpose through chemical action in the body and is not dependent upon being metabolized to achieve its purpose.

Double-blind Study A study in which the neither the subject nor the study personnel know the treatment assignment.

Drug An article (other than food) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

Drug Accountability Records of the receipt and disposition of investigational drug supplies.

Eligibility Criteria Rules for selecting subjects to participate in a clinical trial. Participants must meet all of the inclusion criteria for trial entry and not have any of the exclusion criteria.

Endpoint An indicator measured to assess the effect of a treatment or therapy (an assessment of safety, efficacy, or another study objective). Also called *outcome, variable, parameter, marker, and measure*.

Equipoise Lack of consensus among health care experts regarding which treatment (out of multiple possible treatments) is most beneficial.

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

Exclusion Criteria Rules of eligibility that exclude an individual from participation in a study.

Expedited Adverse Event Reporting Reporting of adverse events designated by the protocol/sponsor to the FDA within specified timeframes.

Federal Register A weekly publication that identifies proposed and approved federal regulations.

Federalwide Assurance (FWA) See *Assurance of Compliance*.

Food and Drug Administration (FDA) A division of the U.S. Department of Health and Human Services responsible for assuring the safety and efficacy of pharmaceuticals, biological products and medical devices, and the safety of foods and cosmetics.

Form FDA 1571 The Investigational New Drug (IND) Application form, which is completed and submitted by the sponsor as part of the IND application.

Form FDA 1572 This "Statement of Investigator" form is completed by all investigators participating in a clinical trial when an Investigational New Drug (IND) application is submitted or an existing IND is updated. By signing this form, the investigator agrees to comply with all regulations pertaining to clinical research. The completed and signed form is submitted to the sponsor, who in turn submits it to the FDA.

Good Clinical Practices (GCP) A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Good Laboratory Practices (GLP) Regulations found in Title 21, Part 58, that apply to clinical laboratories performing analyses for clinical trials. Key provisions of Good Laboratory Practice regulations are requirements for the creation of a quality assurance unit; the development of standard operating procedures; analyses of the investigational product for concentration, uniformity, and stability; and the maintenance, calibration, and standardization of instruments.

Good Manufacturing Practices (GMP) Regulations found in Title 21, Parts 210, 211, and 820. GMP regulations describe the methods, equipment, facilities, and controls required for producing products, devices, and food; the regulations apply to clinical research when pharmaceutical products and medical devices are manufactured and tested. The regulations apply to any drug product intended for administration to humans or animals, including products still in development.

Guidance Documents Explanations that represent the FDA's current thinking on a specific topic. Guidance documents are not legally binding and alternative approaches can be used if the approach satisfies regulatory requirements.

Guidelines Written principles and practices pertaining to the application of the regulations. Guidelines are an accepted standard of practice, however, are not enforceable by law. *FDA guidelines* are applicable in the United States while *ICH guidelines* reflect an international movement to standardize practices across national borders.

HIPAA (Health Insurance Portability and Accountability Act) Law enacted to simplify health care transactions and lower costs by

encouraging health care providers to submit insurance claims electronically. Concern about the security of electronically transferred sensitive health information led to a HIPAA requirement for the development of rules to safeguard the privacy of this information. HIPAA requires that procedures be in place to protect individuals' privacy rights and requires authorization for the use and disclosure of any person's protected health information.

Impartial Witness A person, who is independent of a clinical trial and cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Inclusion Criteria Qualifying rules that a subject must meet to be eligible for participation in a study.

IND Safety Report A report issued by the sponsor of an investigational product when a safety issue arises. The report is submitted to the FDA, investigators, and institutional review boards.

Independent Ethics Committee (IEC) See *Institutional Review Board*.

Informed Consent A process by which a subject voluntarily affirms his or her willingness to participate in a clinical trial after having been informed of all aspects relevant to the decision to participate. The Declaration of Helsinki states that in any research involving human subjects, each potential subject must be adequately informed of the aims, methods, anticipated benefits, potential hazards, and any discomfort study participation may entail. Subjects must be informed that participation is voluntary and that the subject may decline to participate or withdraw from participation at any time without penalty. Informed consent is typically documented via a written *Consent Form*, which the subject signs and dates.

Inspection An official review by regulatory authorities of any study-related documents, facilities, records, or other resources. Inspections may be carried out at investigative sites, at the facilities of the sponsor and/or research organizations performing sponsor-delegated activities, and at other establishments deemed appropriate by the authorities performing the inspection.

Institutional Review Board (IRB) A board, committee, or other group that is responsible for reviewing and approving clinical studies at an investigative site. The primary purpose of the committee's

responsibilities is to ensure the protection of the rights and welfare of study participants. Also called *Independent Review Committee*, *Ethics Committee*, or *Human Protection Committee*.

International Conference on Harmonisation (ICH) A committee established to develop unified standards for data and technical requirements for the European Union, Japan, and the United States, to facilitate the mutual acceptance of clinical data by regulatory authorities in these jurisdictions (full name: The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

Investigational Device Exemption (IDE) Exemption from certain regulatory requirements that apply to medical devices in commercial distribution in order to allow manufacturers to ship devices that are intended solely for investigational use on human subjects. An approved IDE application permits a device that would otherwise be subject to marketing clearance to be lawfully shipped for use in a clinical study.

Investigational New Drug (IND) Application An application that sponsors must submit to the FDA before beginning studies of an investigational drug or biologic in humans. An IND is an application for exemption from the laws that prevent the distribution and use of pharmaceutical agents that have not been approved for use by the FDA. The IND should include a summary and description of the plan for studying the treatment, a summary of any previous human experience with the investigational drug, and should give a complete picture of the drug, including the structural formula, animal test results, and manufacturing information. Also called the *Notice of Claimed Investigational Exemption for a New Drug*.

Investigative Site The clinical setting where a study is being conducted. Site locations include physicians' offices, hospitals, and outpatient clinics. Also known as *Study Site*.

Investigator See *Principal Investigator.*

Investigator-directed Inspection An FDA inspection that focuses on the work of an investigator rather than on a specific study. It may be an extension of a study-directed inspection and may be conducted as a result of questions arising from (or problems encountered during) a study-directed inspection. Formerly referred to as *for-cause inspection*; also see *Inspection*.

Investigator's Brochure A brochure compiled by the sponsor that provides all known information about the test article or investigational

agent. It includes the formulation of the investigational agent, pharmacology and toxicology, pharmacokinetics, safety and effectiveness data, and possible side effects and risks. Both pre-clinical and clinical data are included. Also called *Investigator's Drug Brochure* and *Investigational Drug Brochure.*

Justice One of the three ethical principles described in *The Belmont Report*. Justice refers to the fair and equal distribution of benefits and burdens that arise during clinical research involving human subjects.

Letter of Agreement A letter outlining the terms of the contract between the sponsor and an investigator. Contents of a Letter of Agreement usually include the terms of the study, including the start and anticipated end of the study, payment methods, data confidentiality, publishing requirements, and product liability issues.

Letter of Indemnification A legal document indicating protection or exemption from liability for compensation or damages from a third party. The Letter of Indemnification usually protects the investigator and investigative site from claims by the study participant that harm was caused as a result of participation in the clinical trial. It does not, however, protect the investigator from claims resulting from negligence on the part of the investigator.

Monitor An individual selected by a sponsor to oversee the progress of a clinical investigation. Activities often include site visits to ensure that the investigator is fulfilling the responsibilities set forth in the Code of Federal Regulations; that submitted data are accurate and complete; and that regulatory requirements pertaining to protocol compliance, adverse event reporting, IRB review and approval, and informed consent are met. Also known as a *Clinical Research Associate (CRA)* or *Clinical Trial Monitor (CTM).*

Monitoring Overseeing the progress of a clinical trial to ensure that it is conducted, recorded, and reported according to the protocol, standard operating procedures, Good Clinical Practice guidelines, and applicable regulations.

New Drug Application (NDA) An application submitted to the FDA requesting approval to market a new drug for human use. The contents of the NDA are provided to demonstrate the safety and efficacy of the investigational drug. The application contains information about the class of the drug and the scientific rationale for the drug, its intended use, and the potential clinical benefits. A summary of the clinical data collected is included with the results of the statistical analyses of the clinical trials.

Nuremberg Code A code of ethics developed from the Nuremberg Military Tribunal's decision in the case of *U.S. v Karl Brandt, et al*. The Code includes ten conditions delineating permissible medical experimentation on human subjects. According to this code, humane experimentation is justified only if its results benefit society and is carried out in accord with the basic principles that "satisfy moral, ethical, and legal concepts."

Open-Label Study A study in which the treatment assignment is not "blinded" to the subjects or study personnel; in other words, subjects and investigators are aware of the treatment assignment.

Permission In the context of a clinical trial, when a child's parents or guardians agree to allow the child to participate in clinical research.

Pharmacodynamics (PD) The study of the biochemical and physiological effects of a drug on the body: how the drug is absorbed, moves throughout the body, binds to various structures, and interacts with molecules within target tissues.

Pharmacokinetics (PK) The study of the activity of a drug in the body over a long period of time: how drugs are absorbed, distributed, localized in tissues, and excreted.

Phases of Pharmaceutical Clinical Trials Clinical trials are often categorized into general phases. Test articles may be evaluated in two or more phases simultaneously in different trials, and some trials may overlap two phases. *Phase 0* comprises exploratory IND studies done in small groups of subjects using subtherapeutic doses. *Phase 1* includes early-stage testing in humans to determine safety and pharmacologic effect (how the drug is absorbed, distributed, metabolized, excreted) and duration of action. Subjects are usually healthy volunteers but may be patients with diseases such as cancer or AIDS. *Phase 2* describes studies performed on small group of subjects (100–300) with target disease to demonstrate safety and efficacy. *Phase 3* studies are performed on larger groups of subject (several hundred to tens of thousands) with the disease or condition of interest in order to provide conclusive evidence regarding a therapy's safety and effectiveness for a specific indication. *Phase 4* studies are performed to establish long-term safety and efficacy after FDA marketing approval for a therapy has been given.

Placebo An inactive agent given to a study subject instead of active drug. The placebo often matches the study drug in appearance to keep subjects and investigators unaware of the treatment assignment. This helps maintain the study "blind," thereby avoiding bias resulting from knowledge of the treatment.

Pre-Clinical Trials Animal studies that provide safety data and information about an investigational product's activities and effect. Pre-clinical trials provide a framework for clinical trial (human) testing.

Premarket Approval (PMA) The FDA process for evaluating the safety and effectiveness of class III devices, which are usually defined as those that support or sustain human life, are of substantial importance in preventing impairment of human health, or that present a potential, unreasonable risk of illness or injury.

Principal Investigator (PI) A person who conducts a clinical study and under whose immediate direction the investigational agent is administered, dispensed, or used in a human subject. When an investigation is conducted by a team at a specific location, the PI is the responsible leader of the group and holds regulatory responsibility for the conduct of the trial at the investigative site. A *co-investigator* is a person who shares equal responsibility in conducting the trial at a site.

Privacy Rule Rules to safeguard the privacy of protected health information. The *Standards for Privacy of Individually Identifiable Health Information*, known as the "***Privacy Rule***," was issued in December 2000.

Protected Health Information (PHI) Individually identifiable health information, including demographic data, collected from an individual.

Protocol A document that identifies the plan or "set of rules" for conducting a specific clinical trial and states the objectives, design, methodology, statistical considerations, and organization of a trial.

Protocol Amendment A written description of changes to, or the formal clarification of, a clinical research protocol.

Quality Assurance The planned and systematic actions that are established to ensure that a trial is conducted and data collected and recorded according to the protocol, standards of good clinical practice, and applicable regulations.

Randomization The process of assigning trial subjects to treatment and control groups using the element of chance; random treatment assignments are performed to reduce bias.

Respect for Persons One of the three ethical principles in *The Belmont Report*. Respect for persons requires investigators to treat research subjects as autonomous beings and to protect those subjects who have diminished autonomy.

Risks The possibility of harm or discomfort for subjects participating in a clinical trial.

Serious adverse event (experience) (SAE) An adverse drug experience occurring at any dose that results in any of the following outcomes: 1) death, 2) a threat to the life of the subject, 3) inpatient hospitalization or prolongation of existing hospitalization, 4) persistent or significant disability/incapacity, or 5) a congenital anomaly/birth defect. Important medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they have the potential to jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Single-blind Study A study in which the subject does not know the treatment assignment but the investigator and study personnel are aware of the treatment the subject is receiving.

Source Documents Original documents, data, and records from which subject data forms are completed. Source documents include but are not limited to hospital records, clinic and office charts, laboratory and procedural reports, subject diaries, pharmacy dispensing records, and x-rays.

Source Document Verification Process of comparing data recorded on subject data forms to the data originally recorded on source documents.

Sponsor An individual, company, institution, or organization that initiates a clinical investigation; the sponsor must comply with the responsibilities outlined in the regulations.

Sponsor-Investigator An individual who both initiates and conducts a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a study subject. The obligations of a sponsor-investigator include those of both the sponsor and the investigator.

Standard Operating Procedure (SOP) Detailed written steps or instructions that provide a structure that allows activities to be performed in a consistent manner.

Study Coordinator See *Clinical Research Coordinator*.

Study-directed Inspections (FDA) Inspections conducted periodically to determine compliance with FDA regulations. Generally, the inspections are conducted for a specific drug, device, biologic, or

study as a result of a pending application for marketing approval. Also called *surveillance and routine inspections*.

Subinvestigator A member of a clinical trial team to whom trial-related activities and/or procedures have been delegated by the principal investigator. While some sponsors ask sites to list non-physicians participating in the study in section 6 of the Form FDA 1572, the FDA regards subinvestigators as those individuals authorized by the principal investigator to make medical judgments and decisions regarding study subjects.

Subject An individual who participates in clinical research, either as a recipient of the test article or as a control. A subject may be either a healthy human volunteer or someone with the disease or condition under study.

Test Article Any drug, biologic, or device being tested for use in humans.

Unblinding Determination of the study treatment administered. Unblinding should only occur when subsequent clinical treatment is dependent upon knowledge of the study treatment given.

Unanticipated Adverse Device Effect Any serious adverse effect on health or safety; any life-threatening problem or death caused by or associated with a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unexpected Adverse Drug Reaction An adverse reaction, the nature or severity of which is not consistent with the applicable product information in the Investigators' Brochure for an unapproved investigational product, or on the package insert/summary of product characteristics for an approved product.

Vulnerable Subjects Persons whose willingness to volunteer in a study may be unduly influenced by expectation of benefits, fear of retaliatory response, or lack of ability to understand trial-related issues. Some groups identified as vulnerable subjects are prisoners, children, unborn fetuses, homeless persons, and others incapable of giving consent.

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