

Ethical Mandates and Federal Regulations for the Conduct of Clinical Research

Part 1: Ethical Guidelines

Formalized codes of ethics for the conduct of clinical research are a relatively new invention, largely because the discipline itself is new. However, doctors have abided by professional codes in their treatment of patients since ancient times. Through the Hippocratic Oath, they have sworn to do no harm, to aid the sick, and to protect the privacy of their patients. Physicians who tried innovative treatments were expected to abide by these rules as well. But it was not until the 19th century, during a time of increasing interest in making medicine more "scientific," that clinical research began to blossom as a discipline. The first "code" of research ethics is attributed to American physician William Beaumont (1785-1853). His 1833 guidelines require the subject's voluntary consent and the right to withdraw from any study. But a more formalized response came only after blatant violations of these basic principles.

The Nuremberg Code

Despite the little attention it received when first issued, the Nuremberg Code is one of the most influential statements of ethical principles for research using human subjects. Subsequent guidelines have expanded and qualified these principles, but they have always referred back to the Code. The full text of the Nuremberg Code appears below (Figure A) but 3 basic principles require highlighting:

1. The subject's voluntary and informed consent is required.
2. Risks and harms to the subject should be minimized.
3. The results of the study must be valuable to society.

The informed consent standards outlined in the Code are very strict, reflecting its historical origins as a response to terrible atrocities. "The voluntary consent of the human subject is absolutely essential." Note that the text does not mention the voluntary consent of a parent or guardian. The Code is unequivocal — informed consent is "a personal duty and responsibility which may not be delegated to another with impunity." It also requires that the subject has "sufficient knowledge and comprehension of the elements of the subject matter involved" so as to be able to make an informed decision. This includes knowledge about the purpose of the experiment, the methods used, and any risks and benefits to the subject.

The study must yield fruitful results for society and not be "random and haphazard." The study must also be conducted by qualified investigators using valid methods and procedures, ethically as well as scientifically unsound. Why? One reason is that participants are exposed to some risk, even if that risk is minimal, and there is no reason to expect that the benefit to be gained. Additionally, people who participate in research without their informed consent may reasonably expect that their participation will help to advance medical knowledge.



A prisoner who has been subjected to low-pressure experimentation. KZ Gedenkstätte Dachau, US Holocaust Memorial Museum

Several of the principles stated in the Code directly address potential risks or harms to the subject. In light of the suffering that was inflicted by Nazi physicians, the Code's authors saw a need to spell this out clearly. Risks to the subject should also be minimized. For example, prior experiments should be carried out in animals before moving to humans.

The Declaration of Helsinki

In the early 1960s the World Health Organization recognized, in part because of the Thalidomide tragedy, that greater international cooperation was necessary on standards for the conduct of research. This recognition led to the Declaration of Helsinki, which was adopted by the World Medical Association in 1964.

The Declaration addresses concerns not present in the Nuremberg Code. For example, it recommends protocol review by an "independent committee" and requires that every precaution be taken to preserve confidentiality. Perhaps most important, however, is that the Declaration carries a view of informed consent that has more nuance. In particular, it allows for a legal guardian to consent to participation in research for a subject who is deemed incompetent to consent. See Attachment A for the text of the October, 2000 version of the Declaration of Helsinki.

After the October, 2000 revisions to Helsinki were issued, there was a good deal of discussion regarding what appears to be a blanket prohibition of placebo controlled trials when a proven alternative exists to the article under study. The Declaration, at item 29 states: "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists." Some researchers have argued that because the Declaration requires the patient receive the best possible treatment, then it must also prohibit all use of placebos; others have responded that such an interpretation is too strict. FDA prefers placebo controls even when there is an approved therapy and as long as the subject's health would not be jeopardized and has refused to accept this prohibition.

Federal Guidelines

When the NIH's Clinical Center opened in 1953, NIH leaders instituted a review mechanism to protect human subjects of research that took place within the facility. A subcommittee of the Medical Board and the Clinical Research Committee was formed to review proposed study protocols. This type of review was not unprecedented, but it was certainly not the norm at the time. Typically, the investigator independently made decisions about informed consent and acceptable risks, and clinical researchers did not see their relationship with patients as fundamentally different from the standard physician-patient relationship. The committee functioned much like today's IRBs, except that it had no community or nonscientist members.

The creation of the committee was a progressive step, but its role was rather limited. There was no formal requirement that it examine every protocol. It was up to the investigator to decide whether any potential risk posed to subjects warranted consulting the committee. Clinical Center directors only required formal review for research involving normal volunteers, because this arrangement did not fit the traditional

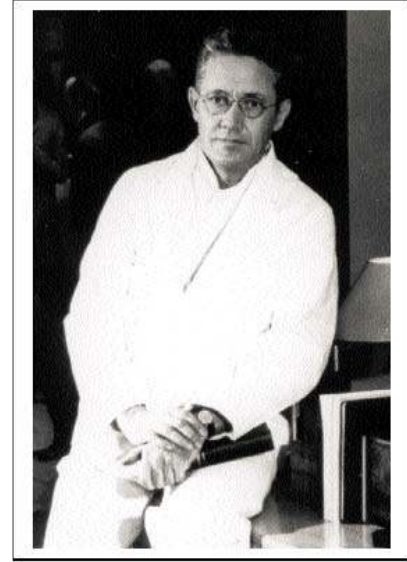
Figure A

The 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, overreaching, 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.
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.

doctor-patient relationship. There were no guidelines for obtaining informed consent, and investigators at the National Institute of Mental Health and the National Cancer Institute reported that formal consent forms were rarely employed and that the information provided was frequently incomplete. NIH intramural researchers tended to view their work as a special case. The Clinical Center, after all, was not an ordinary hospital, and patients were encouraged to believe that they had received an opportunity open to few. Researchers did care about the welfare of patients, of course, but they believed that the investigator was in a better position to make decisions.

However, in March 1965 Henry Beecher, a Harvard Medical School professor, delivered a paper on the ethics of clinical research to attendees at a pharmaceutical conference. Without identifying the researchers, he described 22 research protocols, including 2 that took place at the NIH, the findings of which had been published in various journals, that he believed were ethically problematical. Beecher's exposé received substantial publicity in the news media, including lengthy stories in the New York Times and The Wall Street Journal, and his paper was published the following year in the New England Journal of Medicine.



Henry K. Beecher, MD, an influential researcher at Massachusetts General Hospital, questioned the conduct of biomedical research in the United States.

National Library of Medicine at

In response to Beecher's expose, as well as other well-publicized lapses in medical research sponsored by the Public Health Service. This action indicated a paradigm shift in the attitude of the Public Health Service: The judgment and integrity of physician-investigators alone was no longer sufficient protection of the rights and welfare of research subjects.

The first medical research in the Clinical Center in 1958.
(Photo courtesy of the DeWitt Stetten, Jr., Museum of Medical Research, National Institutes of Health.)

The policy required that no "new, renewal, or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the PHS unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination

- (1) of the rights and welfare of the individual or individuals involved,
- (2) of the appropriateness of the methods used to secure informed consent, and
- (3) of the risks and potential medical benefits of the investigation. A description of the committee of the associates who will provide the review shall be included in the application."

In 1969 the PHS guidelines were revised to require the inclusion of members who could review research in terms of institutional requirements, relevant law, standards of professional practice, and community acceptance.

The guidelines established the IRB mechanism that, for the first time, provided some oversight of research protocols independent of the investigator. NIH policy finally began to acknowledge that research practice did differ from the conventional physician-patient relationship. However, the guidelines did not apply to the NIH intramural program until 12 July 1974 when they became law in the National Research Act (P.L. 93-348).

The Belmont Report

The National Research Act of 1974 aimed to increase biomedical training opportunities and to improve the protection of human subjects in research. The law established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was charged with identifying the "basic ethical principles" that should underlie biomedical research with human subjects. Members of the commission were from diverse disciplines, including biology, law, religious studies, bioethics, and psychology. The commission summarized its conclusions from almost 4 years of ongoing discussions in the Belmont Report, which was released on 18 April 1979. See Attachment B for the text of the Belmont Report.

The commission cited 3 basic principles as being particularly relevant to the ethics of research involving human subjects and used specific examples to illustrate these principles.

↑ 10 Respect for Persons – Having respect for research subjects as persons means respecting their autonomy (their right to make decisions for themselves). Thus, subjects should participate in research voluntarily and be given enough information to make an informed choice. This principle incorporates (as



The first patient is admitted to the Clinical Center in 1953.

(Photo courtesy of the DeWitt Stetten, Jr., Museum of Medical Research, National Institutes of Health.)

established in precedents of Anglo-American law) the autonomy of the individual person. However, not everyone has the same capacity for self-direction. For example, children and some mentally disabled persons have a diminished capacity for effective decision making. The Belmont Report makes it clear that such persons require special protections.

↑ 10 Beneficence – The principle of beneficence imposes two requirements: (1) do no harm and (2) maximize possible benefits and minimize possible harms. Thus, risks to subjects must be balanced against benefits to them and to others. The commission stated that 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.

↑ 10 Justice – The principle of justice requires “fairness in distribution” of benefits. The Report cited the Tuskegee Syphilis Study as a violation of this principle; the “study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population.”

In addition, the commission recommended that the regulations be standardized among all departments of the federal government. On 26 January 1981 (FR 46:8366) and 27 January 1981 (FR 46:8942) respectively HHS and the FDA published their revised regulations to protect human subjects of clinical investigations. Both sets of regulations went into effect on 27 July 1981.

Conclusion

A common misconception about ethics is that it consists simply of a list of “dos” and “don’ts.” Thus, doing the right thing is only a matter of following the rules. But, as the history of research ethics evolves, ethical norms can undergo substantial change. In this regard the practice of ethics is no different from therapeutics. As more information is gathered, old remedies are discarded in favor of those that are newer and more effective. Likewise, history has given us valuable lessons in ethics, and it would be presumptuous to believe that we have nothing more to learn.

Indeed, the most challenging ethical issues remain those where answers are not forthcoming. In some cases it is not clear where to draw the line between research and treatment. Researchers have referred to the “uncertainty principle” — it is ethical, for instance, to recommend participation in a randomized trial only if the physician is unsure which treatment would be better for the patient. But how much knowledge must one have before the study becomes unethical? We will surely continue to rethink our basic principles and to disagree over their interpretation. Additionally, because there is no computer algorithm that can apply these principles in real situations, real people must exercise their judgment on these matters.

Part 2: Informed Consent

Section A: Dialogue and Document

Introduction

Primum non nocere (first, do no harm) is the philosophy fundamental to medical practice. With the burgeoning of scientific investigation in the 19th century, physicians began to assume the dual role of physician/researcher. The reflections of these early pioneering investigators serve as the foundation for ethical standards of behavior in human experimentation. In 1833, William Beaumont, an American physician, began a series of nontherapeutic studies on one of his patients. Dr. Beaumont subsequently detailed for his colleagues guidelines by which to conduct an ethically sound clinical investigation. In addition to a well-designed trial, he stressed the subject's role in the study, calling for informed consent and recognizing the patient's right to withdraw.

Thirty years earlier an English physician, Thomas Percival, grappled with similar issues. He focused attention upon advancement of new therapies and medical interventions that must be grounded in scrupulous technique and competent investigators. In 1865 the physiologist Claude Bernard published *An Introduction to the Study of Experimental Medicine*. This work placed emphasis (albeit at times inconsistently) upon the individual subject at the expense of science. Bernard stated, "Christian morals forbid only one thing, doing ill to one's neighbor. So, among the experiments that might be tried on man, those that can only harm are forbidden. Those that are innocent are permissible, and those that may do good are obligatory." However, risk-benefit determination, according to Bernard, rested not with the subject, but with the

investigator/physician. Reed Army Institute of Research. It is an allegorical dramatizing of

Conquerors of Yellow Fever by Dean Cornwell hangs in the Walter

the first known experimental transmission of yellow fever from a **Walter**

Reed and Yellow Fever mosquito.

Yellow fever was one of the most feared epidemic diseases of the 19th

Depicted are the members of the Yellow Fever Commission who, in

1900 not only experimented on themselves, but also utilized paid

port cities with heavy international traffic, like Havana, the

disease was rampant. U.S. Army physician Walter Reed and his

Spanish volunteers

coworkers on the Yellow Fever Commission, including James Carroll,

Jesse Lazear, and Aristides Agramonte, had begun to study yellow fever

in Cuba in 1900. At the time, investigators disagreed about whether or not the disease was transmitted

by mosquitoes. Reed and colleagues knew that identifying the mode of transmission could lead to

preventive strategies and save many lives.

However, investigators did not have an animal model for yellow fever. Thus, the disease would have to be

studied in humans if it was to be studied at all. Reed proposed an experiment. They would allow human

subjects to be bitten by infected mosquitoes and see whether they developed the disease. Carroll later

described how the group had struggled in early discussions over their moral responsibilities in such an

experiment. They decided to experiment on themselves first, and Lazear died of yellow fever during their

investigation. But they needed more subjects for an effective demonstration.

A grant from the Cuban government allowed them to recruit Spanish immigrants to participate. The Spanish

subjects received 100 dollars in gold, free medical care, and an additional 100 dollars if they contracted yellow

fever. The researchers took the additional step of employing a written consent form. The form, which was

written in English and Spanish, stated that the subject consented to participate "in the enjoyment and exercise

of his own free will." However, it reads as if it was written to persuade, downplaying the risks and exaggerating

the benefits:

The undersigned understands perfectly well that in case of the development [of yellow fever] in him, that he

endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his

stay in this island, he prefers to take the chance contracting it intentionally in the belief that he will receive from

said Commission the greatest care and the most skillful medical service.

Nevertheless, the use of a written consent form was a substantial innovation at the time.

Reed and colleagues may have been motivated in part by fierce criticism of earlier yellow fever experiments by Guiseppe Sanarelli, who exposed subjects to the disease without their consent. Moreover, because exposure to the disease did not serve any therapeutic purpose, the yellow fever experiments were viewed as a special case. Written consent was not to become the norm in clinical research until decades later.

The Legal Viewpoint

A number of cases adjudicated in the courts illustrate the legal perspective regarding informed consent by subjects of human research. Although these suits stemmed from civil cases involving the relationship of the physician and patient in a clinical care setting, decisions supporting informed consent, vis-à-vis disclosure, competency, and risk-benefit assessment, were indeed applicable to the relationship of the investigator and subject in the research setting.

American and English courts took note of human research as evidenced in two cases involving harm to the patient/subject. The earliest case involving experimental treatment was *Slater v. Baker* (2 Wils. K.B. 359, 95 Eng. Rep. 860 [1767]) in England. The court held that the proper practice of medicine required knowledge and application of accepted methods of treatment and that the patient must give his consent after being properly informed.

Another often cited case is *Carpenter v. Blake* (60 Barb. N.Y. 488 [1871]) and again the court held that standard therapies must be used when available. Under the English law, the individual's self-determination is paramount. The law defines the relationship between the physician and patient as a fiduciary one, in which the professional is obligated to provide full disclosure. With regard to experimentation, the courts' precedents were based on cases in which harm had been done to the patient.

Therefore, according to Anglo-American law, a physician experiments at his or her peril. If there is a departure from accepted methods of treatment (the law is not concerned whether this means experimentation or just incompetence), the physician is responsible for any adverse consequences. Once in a court of law, it is the judge and jury, not the physician, who decides what was experimental and what was standard. More important for the future, however, is that "...[t]he language in the early cases suggests that rights of freedom from bodily invasion contain rights of medical decision-making by patients."

The principle of autonomy lies behind the law's interest in informed consent. The legendary Justice Cardozo articulated this principle in 1915: "every human being of adult years and sound mind has a right to determine what shall be done with his own body." The law has recognized this concern for an individual's bodily integrity for some time — since long before the Nuremberg Code — in the context of clinical care. In late 18th century England a patient successfully sued 2 doctors for disuniting a partially healed fracture without the patient's consent. While the classic cases have primarily arisen from clinical care situations, their clarification of the requirement for informed consent is relevant for human-subjects research as well.

Canterbury v. Spence

In December 1958, 19-year-old Mr. Canterbury was working as a clerk at the FBI and began to experience severe pain between his shoulder blades. After some initial tests, Dr. Spence recommended spinal surgery but did not disclose the risks associated with such an operation. The day after the operation, the patient fell, resulting in partial paralysis.

At the initial trial the judge ruled that Canterbury did not have a case because he had failed to show that Spence had been negligent in his care. The appeals court, however, argued that the physician's responsibility does not end with providing competent therapeutic care. The physician is also "under an obligation to communicate specific information to the patient when the exigencies of reasonable care call for it." However, the court recognized that there must be reasonable limits to how much information the physician must provide. In the research context, the IRB examines the consent form to ensure that it includes essential information.

Moore v. Regents of the University of California

Mr. Moore underwent treatment for hairy-cell leukemia at UCLA Medical Center beginning in 1976. As part of his treatment, his spleen was removed and blood samples and other cells were taken. However, Moore's attending physician, Dr. Golde, did not inform him that he was using a portion of the spleen and other cells to create a commercial cell line. Golde was due to profit substantially from the arrangement.

The Supreme Court of California ruled that even if the operation was medically indicated, Golde had a duty to reveal his research and economic interests. In particular, the patient was entitled to know about any potential conflict of interest that might affect the physician's therapeutic judgment. Recent controversies about payments

to doctors for recruiting drug study subjects raise a related issue — are they obligated to inform their patients of their financial benefit?

Capacity to Consent

In 1964, when physicians met in Helsinki to draw up professional guidelines that applied the principles of the Nuremberg Code, the subject of substituted judgment allowing for proxy consent was addressed. The Declaration of Helsinki first recognized the need for a provision allowing for cognitively impaired subjects to enroll in clinical trials, stating: "Clinical research on a human being cannot be undertaken without his free consent, after he has been fully informed; if he is legally incompetent the consent of the legal guardian should be procured."

The issues surrounding capacity to consent affect people who may not be able to fully comprehend enough information about the research to give a truly informed consent. This primarily affects research on children, the mentally impaired (both temporarily and permanently), and those who cannot understand the language in which the information about the research is presented.

The other issue in freely given consent is coercion — whether the subject is in a position, real or perceived, to say no to participation. Groups that might be subject to coercion include anyone whose welfare depends on the individual or group conducting or sponsoring the research, such as prisoners, employees of the investigator, terminally ill individuals, and children.

Section B: Ethical and Regulatory Aspects of Informed Consent

Informed consent is a process, not a single occurrence. Before an individual agrees to be a subject in a research study, the details of the study must be thoroughly explained by a member of the research team who is knowledgeable about the study and has the appropriate education and training in the area being studied. The subject must also be given a written description of the study, which he or she is required to sign before taking part in the research. This document meant to be written evidence that the subject has been informed completely about the research study and understands the ramifications of his or her participation in the research study. Federal regulations set out specific requirements for informed consent, and specify what must be included in the written consent document.

One of the IRB's primary responsibilities is to review the form and ensure that the written document contains all the required elements. However, the subject's signature on a form is not an end unto itself, it is simply documentation that is part of a process that takes place over a continuum.

The regulations promulgated in 45 CFR 46.116 and 21 CFR 50 are based on the Belmont Report, the Declaration of Helsinki, and ultimately on the Nuremberg Code. These are the regulations that describe the elements of informed consent and the general requirements of obtaining consent. These are the federal mandates under which information is provided to subjects and consent documented in the United States and, under the International Conference on Harmonisation (ICH) guidelines, how informed consent will most likely be provided and documented throughout the world.

The Process of Informed Consent

The process of informed consent begins when the anticipated study population is first informed about a research project. It continues through initial contact, usually by phone or during an office visit. If the potential subject expresses interest in participation, the process continues and the study fully explained, the consent document signed, and the subject enrolled. But it doesn't stop there because informed consent is an ongoing process. Every time there is communication between the investigator(s) and subject there is an opportunity for additional questions and explanations.

The process of informed consent begins the moment information about a study is made public. The following is an overview of the process:

- Recruitment advertisements should be clear and straightforward — they should not entice subjects nor should they "sell" participation. IRBs or staff should scrutinize centrally produced advertisements to make sure they are appropriate for their local population. Guidance from the FDA describe criteria for recruitment advertising. Refer to FDA's Good Clinical Practice Program Website for Information Sheets for Institutional Review Boards and Clinical Investigators at <http://www.fda.gov/oc/ohrt/irbs/default.htm>.

- Details of initial contact should be scrutinized. How will subjects be referred to the investigative site? Will centralized recruitment material be used? If a central, professional recruitment company is used, the IRB must review and approve the script, should know the educational background of the individuals conducting the interview, and any details about how interested persons will be handled. Investigators must understand and conform to the institution's requirements regarding recruitment.
- When the individuals come to the research site, the study is explained, in detail, by a responsible, knowledgeable investigator or staff member. For example, when the principal investigator meets with the subject and explains the study, there should be a dialogue, not just a hurried lecture. Then, the study coordinator/research nurse may meet with the individual to continue the discussion. When the potential subject feels comfortable with the details of the study, he or she should be presented with the consent form. The purpose of the consent form should be explained, emphasizing that it is not a contract.
- Depending upon the complexity of the study, capacity of the subjects to understand the risks and procedures of the study, and a number of other factors that may influence subjects' ability to make an informed decision, subjects may be encouraged to take the consent form home and read it with their family. If they read it at the site, they should be left alone with the document and given a way of calling for the coordinator when they are ready to sign the form or not. At this point, they may have more questions. The principal investigator should be available to answer questions, or the research nurse/coordinator may.
- The consent process does not end with enrollment. Each time subjects come to the facility, the investigative team asks whether subjects have any questions, are still comfortable with their participation, and are willing to continue. This discussion should take place after all the study procedures are completed and time can be taken to talk to the subject in an unhurried way.

The Regulations

The general requirements for informed consent are federally mandated and appear at 45 CFR 46.116 and 21 CFR 50.116. Although every consent document must include the mandated information, an IRB may require additional information if it determines that potential subjects need it to make an informed decision about whether or not to take part or to protect subjects' rights and welfare. The mandated elements of informed consent are as follows:

Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

The subjects should be aware that they are participating in research, even if the procedures they undergo provide therapeutic benefit, the purpose of the study is to generate information, not to provide therapeutic benefits. Subjects should understand the goals of the study also.

Participants also need to know the details of what their participation entails in terms of time commitment, the kinds of tests and procedures they will have to undergo, and if any of the tests/procedures are experimental or not part of their standard care.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

Risks and discomforts range from bruising after a blood draw to death from a drug reaction. IRBs sometimes struggle over what a "reasonably foreseeable" risk is. Should subjects be informed of every potential discomfort or inconvenience? Should they be informed of rare reactions that are not clearly linked to the experimental treatment? How much information is too much? The IRB must balance the need to fully inform the research subject against the need to present an accessible consent form.

(3) A description of any benefits to the subject or to others, which may reasonably be expected from the research.

Special care should be taken over what is listed as a "benefit" of participation. For example, it would be misleading to classify standard treatment that the subject would receive anyway as a benefit of participation in the research. It is important to remember that clinical research is not conducted primarily for the benefit of the subject, but to gather data to support or reject a hypothesis.

In addition, if the investigator could benefit from the research, subjects may need to be informed. Subjects should be informed if the investigator stands to gain financially based on the positive results of the research, for

example, if the investigator has been instrumental in the product's development or has an interest in a sponsoring company. Normal compensation for time and expertise is not considered a benefit for either the subject or investigator. (In the case of industry-sponsored studies, in which investigators are often paid per enrolled subject, some IRBs feel that subjects should be informed of this arrangement.)

4) A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject.

If other therapies are available besides the experimental treatment, subjects should be told about those therapies.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. (If an FDA-regulated product is being used, the statement should also note that the FDA may inspect the subject's medical records.)

Subjects should be told who will have access to their personal information (i.e. investigators, contract research staff, the sponsor). Personal information includes medical records, Social Security number, name, address, phone number. They should also be informed of how the records are stored and what measures are being taken to protect confidentiality, such as use of locked filing cabinets. It may also be noted, especially for research subject to FDA oversight, that even if a subject withdraws from a study, the pertinent medical records may still be reviewed.

Under HIPAA, covered entities will need to provide a statement compliant with the Privacy Rule ([45 CFR 164.508(c)] Implementation specifications: Core elements and requirements.) This statement can be combined with the consent document or provided separately.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

A sponsor or investigator is not required by regulations to provide any compensation. However, the extent of compensation, if any, needs to be stated. The institution may have specific requirements for compensation for injury. In any event, the subject should be clearly informed about compensation.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

Often the principal investigator is listed as the contact for questions about research and research-related injury, and the chairperson or other appropriate individual with the IRB is listed as the contact for questions about the rights of research subjects.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The subject should be aware that he or she has agreed to participate in a research study, but is not legally bound by any contract. Thus, it is unacceptable to impose any penalty (or threaten to do so) when the subject fails to follow the directions he or she is given in the study.

Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable. (Note. Only the required elements listed above must be included in every consent document. Out of habit or uncertainty, the additional elements are often included when they are not necessary.)

If the study involves an investigational article that has the potential for serious side effects that are not known, the subject needs to be informed. If there are sufficient data on a study article that indicate there are no risks other than those that have already been explained in the consent form, this statement is not needed. However, unless a compound has been studied in this population, there would be insufficient data about the effects of a

drug or biologic on a fetus or young child, so language about unforeseen effects are often included in a consent form.

(2) Anticipated circumstances under which the subject's participation must be terminated by the investigator without regard to the subject's consent.

These circumstances are listed in most consent forms, and usually specify situations that would require termination from a study.

(3) Any additional costs to the subject that may result from participation in the research.

Generally, subjects cannot be charged for drugs and biologics that do not have FDA approval. However, subjects can be charged for the cost of a device. Subjects should not be charged for study-related procedures that are being performed for the purposes of the study only. However, they can be charged for procedures and tests that would be required in standard care.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

The subject needs to be told what will happen if he or she elects to end participation. For example, that payment accrued for participation will be forthcoming, that the study article will not be available, that it may not be possible to have blood or tissue samples excluded from testing. It is important to let the subject know whether or not his or her records will be subject to examination unless the subject withdraws permission, but that the FDA may examine the subject's medical records regardless. The subject should be told that he or she will be asked to return for a completion visit, but that the subject can refuse to return for such a visit.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

Subjects need to be informed of significant findings that might influence their decision to remain in the study. If no significant findings are anticipated, this language does not need to be included. For example, it is doubtful that significant findings will result from research that is not conducted for safety or efficacy, or in a study of short duration.

(6) The approximate number of subjects involved in the study.

If the IRB feels that knowing the number of subjects that are or will be participating in a study could influence the individual's decision to participate, the number of subjects should be stated. For example, it is probably not necessary to indicate the number of subjects in a large, multicenter phase 3 study. However, if there will only be a few subjects taking part, in a phase 1 or 2 study or early phase 3, this may be pertinent. It is actually more informative for a subject to know how many subjects have already been exposed to a study article. Even in a study of 500 people, a person may want to know if only 20 people have ever been exposed to a product at the time he or she is being enrolled in the study.

Conclusion

Informed consent is a process in which the researcher and subject interact on a continuum. Because signing the consent document is pivotal to the process, it is important that the consent form be understandable to the subject. The form should be composed in a language that is at an appropriate educational level for the anticipated study population and it should be in a language well understood by the subject.

The aim of the consent process, after all, is to protect the interests of the subject not those of the investigator, sponsor, or institution. The consent form, therefore, should provide evidence that the welfare of the subject was primary by being easy to read and free of unexplained medical terms and awkward legalistic phrases.

Part 3: Good Clinical Practice (GCP)

In recent years, international GCP standards have emerged in an effort to harmonize research efforts, reduce waste, and expedite approval. The United States, European Union, and Japan have joined forces at the International Conference on Harmonisation (ICH) to develop global standards for the conduct of clinical research. The purpose of ICH is to facilitate mutual acceptance of data submitted in support of drug marketing applications. Their GCP guideline (E6) was printed in the Federal Register on 9 May 1997. While this document was not incorporated into the Code of Federal Regulations, and therefore does not carry the weight of law, it has been adopted by industry and academia worldwide. With all countries conducting research according to the same standards, duplication of effort and resources should be minimized.

ICH defines GCP as, "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." This definition accurately captures the whole of GCP, both data integrity and subject protection, and specifies areas of trial implementation that directly affect GCP.

The pillars of GCP are protection of subject's rights and promotion of data integrity. These two principles provide the foundation for ethically and scientifically sound research, both of which are crucial to the overall success of a trial. Positive data results will not be published if they were gained in an unethical manner, just as the results of a well-conducted study will be inconclusive if the design was flawed.

Subject's rights are outlined in 21 CFR 50 and 56, 45 CFR 46, FDA Information Sheets, ICH GCP (E6), ICH General Considerations (E8), Nuremberg Code, Declaration of Helsinki, and Belmont Report, which define informed consent requirements, IRB requirements, investigator qualifications, study design, and basic ethical principles. Most of the basic human subjects protections such as informed consent requirements and IRB review and approval, are well known. However, more subtle violations of subject's rights exist. For example, the design of a study can have serious ethical implications. A randomized study comparing an approved medicine to an investigational compound may infringe on subjects' rights by exposing them to unnecessary risk.

Data integrity standards are outlined in 21 CFR 56 and 312, FDA Information Sheets, ICH GCP (E6), ICH Statistical Consideration (E9), Nuremberg Code, and Declaration of Helsinki. These documents outline study design standards and responsibilities of sponsors and investigators, including data monitoring, ongoing study review, source documentation verification, and adverse event reporting.

Assurance of data integrity begins from the moment the protocol is conceived. For example, study design can influence data in a number of different ways. Poor study design can lead to bias, confounding variables, or weak statistical conclusions. Lack of effective monitoring by the sponsor could lead to a failure to recognize inaccurate or fraudulent data. Poor protocol design or erroneous data, if not discovered in time, would pose a threat to the general population by either allowing the introduction of a new drug that is not safe and/or effective or delay the availability of beneficial therapy because additional studies must be conducted.

ICH GCP guidelines contain more detailed information than any other GCP guidance document to date. Where FDA talks generally about roles and responsibilities, ICH GCP provides more detail. For example, the second heading in ICH GCP outlines 13 principles of GCP. While all of these principles are mentioned in FDA regulations, they are scattered throughout different parts of Title 21 and not specifically defined as GCP principles. The ICH, in writing the E6 GCP guideline, has recognized the need for detailed written instructions for how to conduct clinical research. In addition, ICH GCP contains a detailed table of essential study documents, their purposes, and where these documents should be kept, either in the sponsor files, the investigators files, or in both. These two examples highlight the detail oriented nature of ICH and illustrate the need to include it in any GCP training program.

Compliance

A review of more than 226 investigator audits, performed by an independent auditing group, revealed the level of GCP compliance to be consistently around 64%. While it is unrealistic to expect perfect compliance at all sites, this rate could be improved. The one factor that affected the level of site compliance was presence of a sponsor's standard operating procedures (SOPs), with compliance rates varying from 43% to 79%. The authors reasoned that sponsor SOPs were a good predictor of investigator compliance, with sponsoring companies having well defined standards being more apt to promote GCP standards at the site.

The same group summarized compliance on a qualitative level, and has provided a view of the types of noncompliance and the seriousness of the infractions at the same 226 sites. Noncompliance was divided into ethical and data integrity subheadings. The most serious noncompliance violations were rated G1 for anything that created a dangerous situation for study subjects, allowed a product to enter the market without proof of safety or efficacy, caused regulatory authorities to reject the study, required all or some of the data to be excluded from analysis, or resulted in sanctions. The less serious noncompliance (G2) refers to occurrences that could lead to an unsafe situation.

The percentage of sites with G1 noncompliance for ethical issues was small, under 3%. However, the percentage of G2 infractions was comparatively high. At 81% of the sites, serious adverse events (SAEs) were either not reported or inadequately reported to the IRB. Also, 38% of the sites implemented protocol amendments without first receiving IRB approval.

Data integrity results were even worse. Thirty-one percent of the sites demonstrated a 10-20% discrepancy between source documents and data collected, which was considered a G1 violation. At nearly one-third of the sites, source documents failed to support the selection of suitable study subjects, also a G1 violation. Less serious infractions (G2) included failure to notify the primary care physician of subject participation (71%), inadequate documentation of subjects exposure to study drug (57%), and lack of proper documentation for changes to study data (47%).

Conclusion

While FDA regulations define GCP, there are numerous guidelines and codes, in addition to federal regulations, that also dictate standards in the conduct of clinical research. For example, the Declaration of Helsinki is often cited as the basis for the protection of human subjects even though it was never formally adopted into federal regulation. GCP is more than a set of regulations; they are concepts that, when combined, serve as the gold standard in the practice of clinical research.