4 Informed Consent and the Regulations

In this Chapter

- What is informed consent?
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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

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 **E**xample of **A** **T**rial

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

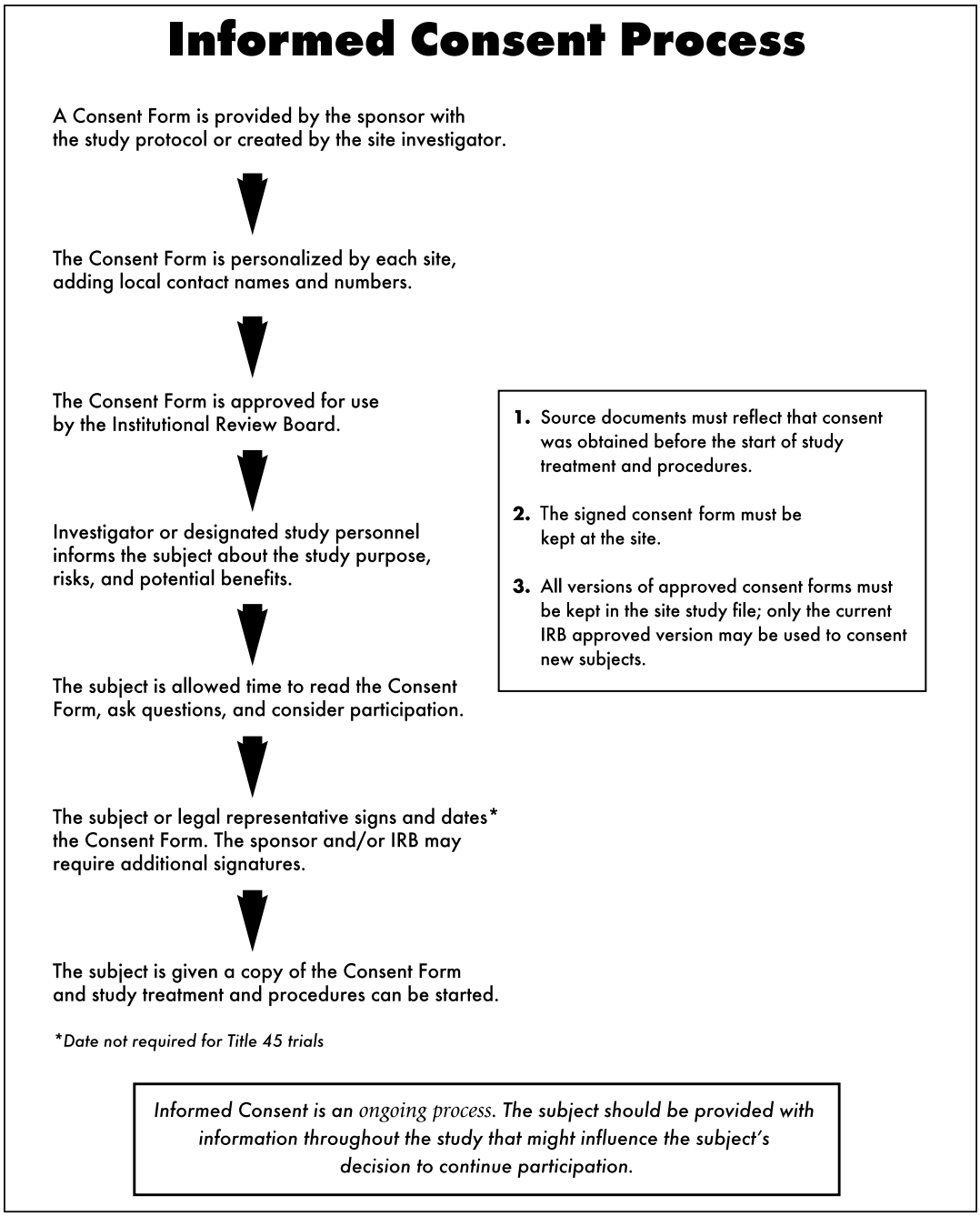
It is important for both the investigator and the study subject to understand that informed consent is an ongoing process that does not end with a signature on a written consent form, but continues through completion of study procedures and follow-up. Study subjects should be informed about the occurrence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

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