

# Informed Consent, Confidentiality, and Subject Rights in Clinical Trials

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The informed consent process is designed to inform the subject of the risks, rights, and benefits of participation in a clinical research trial. Informed consent, while not always necessary, is a critical component of ethical research involving human subjects. This article includes an overview of two sets of regulations regarding informed consent found in the Code of Federal Regulations (CFR) Titles 21 and 45: 21 CFR 50 and 56, the Food and Drug Administration Regulations, and 45 CFR 46, where applicable, the Department of Health and Human Services Regulations. Also included in this discussion are the general requirements of informed consent; challenging issues regarding informed consent; determining and obtaining informed consent in research involving vulnerable subjects (e.g., children, critically ill patients); the use of genetic information; confidentiality and privacy of subject information; and compensation for injury during a research study. Examples of acceptable and unacceptable (exculpatory) informed consent language are also provided as they may pertain to commercial gain, confidentiality, and compensation for injury. The goal of this article is to provide the clinical researcher with an explanation of the legal requirements for informed consent in clinical research. The researcher faces many challenges in implementing effective informed consent beyond the federal regulations.

**Keywords:** ethics; clinical trial; vulnerable populations

## INFORMED CONSENT

In 1979, the Belmont Report was issued in the United States. This report summarized the basic ethical principles identified by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was established as a result of the National Research Act in 1974. Three major principles emerged from the Belmont Report: beneficence, justice, and respect for persons. This article will focus on the principle of respect for persons. From the principle of respect for persons, the individual is viewed as an autonomous agent (capable of self-determination); therefore, humans as research subjects should be given the opportunity to choose whether they will participate in clinical research. This is accomplished through the process of informed consent (which encompasses not only the informed consent document but also, importantly, verbal discussions with the potential subject). This concept of autonomy also implies that people with diminished capacity (or diminished autonomy) are entitled to additional protection. The Belmont Report also discusses the voluntary nature of informed consent and explains that the information must be complete, understandable, and presented in an unhurried fashion. Importantly, the investigator is responsible for determining whether the subject

really understands this information. How is the potential subject's understanding measured? Some investigators give short tests on the information; some investigators ask for verbal feedback; and some simply ask the subjects if they understood the information presented.

In the United States, there are 2 sets of regulations regarding informed consent: regulations found in the Code of Federal Regulations Titles 21 and 45: 21 CFR 50 and 56, the Food and Drug Administration (FDA) regulations, and 45 CFR Part 46, where applicable, the Department of Health and Human Services (DHHS) Regulations (1–3). Many of the informed consent regulations are identical, but there are some differences. This article will focus on the FDA regulations. Of note, the goal of this article is to provide the clinical researcher with an explanation of the legal requirements for informed consent in clinical research. The researcher faces many challenges in implementing effective informed consent beyond the federal regulations.

## GENERAL REQUIREMENTS OF INFORMED CONSENT

Informed consent must be obtained from the subject or, if appropriate, the subject's legally-authorized representative (LAR) under circumstances that minimize the possibility of coercion or undue influence. The information should be in a language that is understandable to the subject, which may necessitate translation of advertisements, the informed consent document (ICD), and other study-related materials, and/or, if necessary, having someone on site who can answer questions. The ICD cannot contain exculpatory or "release" language; that is, the ICD language cannot waive or appear to waive any subject rights or to release or appear to release the investigator, the sponsor, or the institution or its agents from liability for negligence (4).

The ICD should state that the study involves research, explain the purpose and expected duration of the study, and describe the procedures that the subject will undergo during the study. The ICD should also include a description of reasonably foreseeable risks, the benefits of the research to the subject or others, alternative treatments, and confidentiality of records (discussed below), noting that the FDA may inspect the records.

The regulations require that, in research involving more than minimal risk, potential subjects be told whether any medical treatment or compensation are available if an injury occurs, and, if so, what they are or where more information can be obtained. Of note, the regulations do not mandate medical treatment and/or compensation for injury, but only require that the ICD indicate whether such treatment and/or compensation is available. The ICD also must identify who the subject can contact if she/he has questions about research, subjects' rights, or any research-related injury, and it must inform the potential subject that participation is voluntary and the subject is free to withdraw from the study at any time. Subjects are not required to undergo any type of final testing or evaluation if they withdraw early; however, they may be asked to do so.

Informed consent, while not always required by federal regulations for ethical research, is a critical component of most research. In certain circumstances, informed consent can be waived, but those situations are very specific. Importantly, an

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institutional review board (IRB) may decide that fully informing subjects of risks—for example, the risk(s) of discontinuing corticosteroids to qualify for an asthma study—does not make ethical the withholding of medication that is appropriate under the relevant standard of care or medication that has documented efficacy.

The FDA considers advertising to be the first step in the informed consent process. Advertising text should, therefore, be consistent with information that is provided in the approved ICD. An advertisement should state that the study involves research and indicate if the drug or device is investigational or experimental. It should neither state nor imply that subjects will receive free medical care. No claim should be made, either explicitly or implicitly, that a drug, device, or biologic is safe or effective for the purposes under investigation.

### CHALLENGING ISSUES REGARDING INFORMED CONSENT: VULNERABLE SUBJECTS

The federal regulations state that even immature or mentally incompetent persons must be given the opportunity to choose, to the extent they are able, whether to participate in research. These and other “vulnerable” persons, however, may participate only if proper safeguards are in place. Table 1 provides a list of people who might be considered vulnerable subjects. Regarding pregnant women and prisoners, the FDA and DHHS regulations differ. While the FDA does not address these populations, the DHHS regulations contain mandatory safeguards that must be in place before pregnant women or prisoners may participate in human subjects research.

One responsibility of an IRB is to determine the level of risk in a research study. For children, the IRB must make and document specific findings regarding risks and anticipated benefit (or lack thereof) to the child subject. An IRB can approve a study involving children only if the study satisfies the regulatory criteria. The FDA criteria related to safeguards for children in clinical investigations are documented at 21 CFR Subpart D Sec. 50.50–50.55. (This discussion will focus on the FDA criteria, but the DHHS criteria can be found at 45 CFR Subpart D Sec. 46.401–46.408.)

If a study does not involve more than minimal risk—that is, the probability and magnitude of harm or discomfort anticipated in the research is not greater than those ordinarily encountered in daily life during the performance of routine physical or psychological examinations or tests [21 CFR 50.3(k)], the IRB must find and document that adequate provisions are made for soliciting the assent of the children and permission of the parents or guardian. For studies that involve greater-than-minimal risk that have a prospect of direct benefit to the subjects, the IRB must

**TABLE 1. PEOPLE WHO MAY BE CONSIDERED VULNERABLE SUBJECTS IN CLINICAL RESEARCH**

- Children
- Economically disadvantaged
- Educationally disadvantaged/illiterate
- Employees
- Physically impaired
- Life-threatening condition/seriously debilitating illness
- Mentally disabled/cognitively impaired
- Non-English-speaking subjects
- Nursing home residents
- Pregnant women
- Prisoners
- University students
- Wards of the State

find and document that the risk is justified by the anticipated benefit to the subject, and the relation of the anticipated benefit to the risk is at least as favorable to subjects as that presented by available alternative approaches. When parental permission is to be obtained, the IRB may find that permission of one parent is sufficient. In addition, adequate provision must be made, when appropriate, for soliciting the assent of the child.

For a study involving greater-than-minimal risk and no prospect of direct benefit, the IRB must initially determine that the risk represents a minor increase over minimal risk. Not surprisingly, the definition of “minor increase over minimal risk” causes significant discussion among IRB members. The IRB must also determine that the research experiences of subjects are reasonably commensurate with their actual or expected medical, dental, psychological, social, or educational situations. The intervention must also be likely to yield generalizable knowledge about the subject’s disorder or condition that is of vital importance to the understanding or amelioration of the subject’s disorder. Again, adequate provision must be made for soliciting the assent of the children and, with a few exceptions, permission of both parents. (For studies that do not fit within the above criteria, 21 CFR 50.54 and 45 CFR 46.407 outline the very specific procedures to be followed during the review of such studies.)

### ASSENT OF CHILDREN IN RESEARCH

“Assent” is defined in the federal regulations as “...a child’s affirmative agreement to participate in a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as assent” (1). A child’s assent should generally be obtained from any child who has the intellectual and emotional ability to understand the concepts that are involved. Thus, an IRB may waive the assent requirement for very young children (e.g., ages 0–6 years), while requiring more mature children (e.g., ages 7–11 years old) to sign a separate assent written at a level appropriate to their intellectual age. A child must affirm that he/she wants to participate, as failure of a child to object is not to be construed as assent. Children ages 12 and older may read the main ICD. Under Alabama and Nebraska state law, 18-year-olds are considered children who require parental permission and who must assent. Of note, persons with low literacy levels are considered to be a vulnerable population, so the IRB should require safeguards before approving the site when these subjects are involved in the research.

In making a determination of whether a child is capable of understanding the ICD, the IRB must take into account the age, maturity, and psychological state of the child involved. Assent is not a necessary condition for proceeding with the study if the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or the intervention holds out a prospect of direct benefit that is important to the health of the children and is only available in the context of the study.

Under the regulations, the IRB can waive assent if it finds and documents that the study involves no more than minimal risk, that the waiver will not adversely affect the rights and welfare of the subjects, that the study cannot practicably be performed without the waiver, and that the subjects, when appropriate, will be provided with additional pertinent information after they have participated.

### CRITICALLY ILL SUBJECTS

For a critically or seriously ill subject, as with all other potential subjects, the investigator must explain fully any available alternative treatments, and explain that the study treatment may or may

not benefit the subject's present condition. The investigator must also confirm that the subject understands this information. If, however, a particular subject is not capable of understanding verbal and written information because of his or her condition, the IRB may approve the use of a legally authorized representative (LAR). The informed consent regulations provide a definition of LAR (i.e., an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures[s] involved in the research [21 CFR 50.3(l)]), thus, the actual determination of who constitutes an LAR is a matter of state law.

In certain cases, critically or seriously ill subjects, such as a subject in the intensive care unit who is too sedated or simply too sick to read and discuss the full-length consent document, can be consented with a "short form" of the ICD. The short form must contain the required elements of the full ICD and all of the elements must be communicated verbally to the potential subject or, if appropriate, his or her LAR. The IRB must approve a written summary of what is to be said to the potential subject or LAR. The oral presentation must be witnessed and the subject or LAR must sign and date the short form, along with the witness (who also signs the summary). A copy of the short form and summary must be given to the subject and/or LAR.

## GENETIC INFORMATION

Table 2 lists information that should be included in an ICD for studies involving genetic research, for example, in which biological samples are collected and used to study subjects' DNA. Use of the word "donation" or "donate" should be avoided. With regard to "donation" of biological specimens, the FDA, in its Information Sheets, states, "The word 'donation' implies abandonment of rights to the 'property'....Whether or not the wording is contained in 'the actual consent form' is immaterial. All study-related documents must be submitted to the IRB for review. Any separate 'donation' agreement is regarded to be part of the informed consent documentation, and must be in compliance with 21 CFR 50" (5).

## EXCULPATORY LANGUAGE IN GENETIC RESEARCH

The informed consent regulations state that no informed consent, whether oral or written, may include any exculpatory language through which the subject or the subject's representative is made to waive or appear to waive any of the subject's legal rights. This is particularly important in pharmacogenetic or pharmacogenomic research, as the ICDs in these studies frequently include "Commercial Gain" statements, indicating the sponsor's plans to develop new products, including its plans as to any

**TABLE 2. INFORMATION RECOMMENDED FOR INCLUSION IN THE INFORMED CONSENT DOCUMENT FOR STUDIES INVOLVING GENETIC RESEARCH**

- What specimens will be studied?
- How and where will specimens be obtained?
- Will specimens be stored for future, presently undefined study?
- Might these studies result in any commercially valuable products?
- Will samples be anonymous?
- How will confidentiality be maintained?
- What will be done with the information obtained on individual subjects?
  - Will results be reported to the subject/parents/relatives?
  - Will results be reported to the attending physician?
  - Will results be recorded in patient's medical record?
- Will there be prospective follow-up contact with the subjects?

profit realized from the commercialized products. Table 3 lists several examples of both acceptable and unacceptable language in ICDs regarding commercial gain statements (4). Words such as "By signing you understand and agree..." should raise a red flag. In fact, the 45 CFR 46.116 states that, "No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence" (3). Informed consent documents should contain statements describing the research, for example, "The sponsor will use your sample to conduct this research," and other language required by the regulations. Language suggesting that the subject has agreed to all of the provisions, for example, "I understand and agree that I will have no right to the samples I have donated," must not be included.

## CONFIDENTIALITY AND PRIVACY IN GENETIC RESEARCH

Confidentiality of subjects' study-related medical records is especially important in studies involving genetic research. (The Health Insurance Portability and Accountability Act [HIPAA] Privacy Rule became effective in 2003; thus, for healthcare providers covered by the HIPAA law, informed consent involves not only confidentiality of subject records but also privacy of subjects' identifiable health information [or "protected health information"], which is broader than records only. It is any health information from which a person can be identified [and there are 18 identifiers such as name, medical record number, some zip codes].) The informed consent regulations require that every ICD have a statement describing the extent to which records that identify the subject will be kept confidential, noting that

**TABLE 3. EXAMPLES OF UNACCEPTABLE EXCULPATORY LANGUAGE AND ACCEPTABLE LANGUAGE IN INFORMED CONSENT DOCUMENTS REGARDING COMMERCIAL GAIN**

### Examples of Exculpatory Language

- By agreeing to this use, you should understand that you will give up all claims to personal benefit from commercial or other use of these substances.
- I voluntarily and freely donate any and all blood, urine, and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items.
- By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research.
- I waive any possibility of compensation for injuries that I may receive as a result of participation in this research.

### Examples of Acceptable Language

- Tissue obtained from you in this research may be used to establish a cell line that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.
- By consenting to participate, you authorize the use of your bodily fluids and tissue samples for the research described above.
- This hospital is not able to offer financial compensation nor to absorb the costs of medical treatment should you be injured as a result of participating in this research.
- This hospital makes no commitment to provide free medical care or payment for any unfavorable outcomes resulting from participation in this research. Medical services will be offered at the usual charge.

<http://www.dhhs.gov/ohrp/humansubjects/guidance/exculp.htm>.

The "acceptable" language uses the words, "use of..." without stating that the sponsor "owns" the sample or that the subject is "donating" the sample. It is recommended that the Commercial Gain statement be followed with a "legal rights" statement, such as, "You do not give up any of your legal rights by signing this document."



**TABLE 4. SAMPLE CONSENT LANGUAGE REGARDING CONFIDENTIALITY**

Records of your participation in this study will be held confidential except as disclosure is required by law or as described in this informed consent document (under "Confidentiality" or "Authorization to Use or Disclose Protected Health Information"). The study doctor, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and the Institutional Review Board (IRB), will be able to inspect and copy confidential study-related records which identify you by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, you will not be identified.

For genetic studies:

Information identifying you will not be included with your blood sample for this research. The link between your identity and your sample will be destroyed before your genes are studied. Therefore, your identity will never be revealed to anyone or be connected with genetic information from your sample. Neither you, nor the study doctor will be able to know the results of any genetic analyses performed on your sample.

the FDA may inspect the records. Table 4 provides sample ICD language for confidentiality, including language for genetic studies. In addition to the confidentiality section of the ICD, most ICDs contain either a combined or separate HIPAA Authorization to Use and Disclose Protected Health Information. For the Authorization to be valid it has to contain certain essential elements: a complete description of any protected health information to be used or disclosed in the study; identification of a person or class of persons authorized to use and disclose protected health information; a description of each purpose for the use of disclosure; either an expiration date or a statement that there is no expiration date; the individual's signature and date; and a description, if signed by an LAR, of the LAR's authority to act on an individual's behalf. The authorization should also contain certain statements regarding: the subject's right to revoke the authorization at any time; how to revoke the authorization; the consequences of refusal to sign an authorization for research; and the potential for the private health information to be re-disclosed by the recipient. The authorization should also state that the subject has a right to see his/her private health information but may not do so until the study sponsor has completed its work related to the study, particularly if the study is blinded.

Guidance from the National Bioethics Advisory Committee states that disclosure of research results to study participants should be an exceptional circumstance and occur only when all of the following apply: (1) the findings are scientifically valid and confirmed; (2) the findings have significant implications for the participant's health concerns; and (3) a course of action to ameliorate or treat these concerns is readily available. This recommendation provides guidance but is not in the form of a regulation enforceable by law.

The researcher should inform potential subjects, via the consent process, and document whether they and/or their physicians will be informed of genetic research results. Risks related to disclosure of genetic results must be explained in plain language during the consent discussion and in the ICD. This is important because information derived from subjects through research may be potentially relevant or it may constitute speculative data of little relevance to the subject. The risks related to disclosure of genetic results, including possible discrimination in obtaining or maintaining employment or insurance coverage, should be considered and disclosed to the potential subject.

**TABLE 5. EXAMPLES OF UNACCEPTABLE (EXCULPATORY) AND ACCEPTABLE LANGUAGE IN INFORMED CONSENT DOCUMENTS REGARDING COMPENSATION FOR INJURY**

Unacceptable Language

- I understand and agree that I will not be compensated if I am injured while participating in this study and I wave any claim I may have against the sponsor or study doctor for such injuries.
- I understand that I will be responsible for my own medical bills if I suffer a research-related injury.
- I release the sponsor and anyone working for the sponsor to conduct this study including my study doctor from any and all liability for any injury I may experience from taking the study drug or undergoing any study procedures.

Acceptable Language

The sponsor makes no commitment to provide free medical care or payment for any injury resulting from your participation in this research study; however, you do not give up any of your legal rights as a research subject by signing this consent document.

The hospital and your study doctor offer no financial payment or reimbursement for medical expenses should you be injured as a result of taking the study medication during this research study; however, you do not give up any of your legal rights as a research subject by signing this consent document.

The language that should signal a red flag is underlined.

## COMPENSATION FOR RESEARCH-RELATED INJURY

The regulations at 21 CFR 50.25 (a) (6) require that, "For research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatment is available if injury occurs and, if so, what they consist of, or where further information may be obtained." Examples of unacceptable and acceptable "compensation for injury" language in the ICD are listed in Table 5.

The American Medical Association's Ethical Guideline E-8.0315(5) states, "Physicians should ensure that protocols include provision for the funding of subjects' medical care in the event of complications associated with research." This guideline also indicates that a physician should not bill a third-party payer when the physician has received funds from the sponsor to cover the additional expenses (6).

## CONCLUSION

The informed consent process is designed to inform the human research subjects of, among other things, the risks, rights, and benefits of participation in clinical research studies. Informed consent, while not always necessary, is a critical component of ethical research involving human subjects. Unless a subject is presented with and understands the various elements of the study through the informed consent process, the subject cannot exercise his or her right to make that informed decision to participate in a research study. The challenge of determining whether the subject truly understands the research project and its risks and benefits remains, even when the legal requirements are met.

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## DISCUSSION HIGHLIGHTS

### Independence of IRBs

DR. ZAB MOSENFAR (*Cedars-Sinai Medical Center, Los Angeles, CA*): To whom do IRBs answer—the institutional legal system, the institution's presidents? To whom *should* they answer?

MS. SMITH-TYLER: The federal regulations state that the IRB should be independent. Certain IRBs are totally independent, but some IRBs report to an institutional official. The regulation says that that the institutional official or institution cannot approve research if it has not been approved by an IRB.

DR. MOSENFAR: Hypothetically, if an IRB chair discovers (or is notified by an investigator) that some egregious event (i.e., research-related injury or death) took place, which would be the institution's downfall should the lay press find out, who should IRB chair go to—the president of the institution, who really has a fiduciary responsibility to protect the institution? What happens next?

MS. SMITH-TYLER: The IRB is responsible for considering any serious adverse events, and the investigator should determine whether or not it was related. The most likely party to be sued is the university or institution of which the IRB is a part; however, the IRB and its members could also be named as defendants in a lawsuit. So, I don't see anything wrong with letting the university know what's going on. The sponsor would also need to know.

DR. MOSENFAR: To me, the IRB is independent. If the IRB chair notifies the institution's president, the president is will want to involve their legal team, to get a handle on the situation. From my perspective, the IRB chair needs to stop the study, talk to the families, and say, "We are accountable."

MS. SMITH-TYLER: With a serious adverse event, everything should be done just like it normally would: report to the sponsor, report the SAE, do everything the IRB is supposed to do. As to telling families "We are accountable," it depends, I guess, on who actually is accountable. Did the IRB do something it should not have done or fail to do something it should have done, or was the SAE related solely to the study drug? If so, did the IRB follow up appropriately? In any event, openness, and never a cover up, is appropriate.

DR. ROBERT A. WISE (*Johns Hopkins University School of Medicine, Baltimore, MD*): But who should manage that process? If the institution manages it, they are going to be protecting themselves. If someone else manages, they are more likely to be impartial.

MS. SMITH-TYLER: Well, some things warrant stopping a study. It may be a situation in which the appropriate government agency, such as the FDA, needs to be notified. There are certain things that an IRB is required to report to the FDA, such as suspension or termination of IRB approval of research.

DR. MOSENFAR: Should there be an ombudsman, or ombudsmen, to whom the research subjects could go if they feel that they need a better understanding the process?

MS. SMITH-TYLER: Under the regulations, you have to tell the subject who he or she can contact with any questions about rights or concerns. We typically give the IRB's phone number, or say (paraphrasing), "You can go to the study doctor if you have a concern about an injury; if you have questions about your rights as a research subject, or complaints about the study, contact the IRB."

### Waiver of Informed Consent Rules

MS. SMITH-TYLER: The FDA doesn't provide for waiver of informed consent, which makes sense because most of the studies under its jurisdiction involve investigational devices or drugs and more than minimal risk. If we have a study that comes under the DHHS regulations [45 CFR 46], there are four basic requirements: The research must not involve more than minimal risk to subjects; waiving or altering informed consent will not adversely affect the rights and welfare of subjects; the research could not practicably be performed without the waiver or alteration; and when appropriate, the subjects must be provided with additional pertinent information after participation. The FDA does allow the administration of an investigational test article provided that such emergency use is reported to the IRB within five working days and that any subsequent use is subject to IRB review.