REVIEW

CME CREDIT

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A guide to informed consent for clinician-investigators

ABSTRACT

Informed consent in clinical research is a matter of both ethics and federal regulation. A research subject must enter a study voluntarily, be informed about risks and benefits, and understand the difference between experiment and treatment.

KEY POINTS

Financial conflicts of interest must be disclosed to federal research agencies, and they pose ethical and potential legal problems in privately funded studies.

An inherent conflict of interest exists when an investigator is the personal physician of study subjects and takes on the dual role of both caring for and performing research on a patient.

As part of the consent process, study subjects should be told about conflicts of interest and risks of the intervention.

Consent forms should use simple language, be noncoercive, and avoid implying that participation will provide a benefit that is not projected to exist.

INFORMED CONSENT is a process, not a form. It is a legal and ethical safeguard to ensure that subjects enter studies voluntarily and fully informed about the nature of the research project.

This article covers ethical and legal guidelines in the consent process, potential conflicts of interest that arise when an investigator is also the subject's physician or has financial stakes in a study, and guidelines for creating consent forms.

ETHICAL AND LEGAL GUIDELINES

From an ethical perspective, informed consent for clinical research requires three elements. The participant must:

- Be informed about the study, including risks and benefits
- Understand the information
- Enroll voluntarily.[1]

From a legal perspective, the United States Code of Federal Regulations (45 CFR §46.116) regulates the informed consent process in clinical research, and investigators should refer to it when creating consent documents. The code defines eight general elements (TABLE 1), as well as additional specific ones that may apply to certain research projects or subjects (eg, pregnant women).

CONFLICTS OF INTEREST

Financial conflict

Regulations specifically exist regarding financial conflict of interest, ie, when a researcher's private interests are (or appear to be) in conflict with official duty requirements. The conflict raises the possibility that a researcher's

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TABLE 1

Elements of informed consent

Basic elements

- Statements indicating that the project is research, the purpose of the research, the expected duration of the subject's participation, and a description of the procedures involved and which procedures are experimental
- A description of the foreseeable risks and discomforts of participating
- A description of the foreseeable benefits to the subject and society
- A disclosure of possible alternatives to participating in the study
- A statement regarding the extent of how the subject's confidentiality will be preserved
- Statements regarding compensation, treatment following injury, and where further information can be obtained
- Statements about whom to contact about the rights of research subjects, as well as whom to contact in case of a research-related injury
- Statements that participation is voluntary, that refusal to participate will not result in penalties or loss of benefits, and that subjects may withdraw from the study at any time without penalties or loss of benefits

Additional elements (as appropriate)

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
- Any additional costs to the subject that may result from participation in the research
- The consequences of a subject's decision to withdraw from the research, and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject
- The approximate number of subjects involved in the study

FROM UNITED STATES CODE OF FEDERAL REGULATIONS (45 CFR §46.116), WWW.HHS.GOV/OHRP/HUMANSUBJECTS/GUIDANCE/45CFR46.HTM#46.116.

personal interests may supersede the best interests of the research subject and the responsible conduct of the research.

For studies sponsored by the National Institutes of Health (NIH), investigators must disclose "significant financial interests" that might be affected by the research. A significant financial interest is defined as anything of monetary value that exceeds $10,000 and represents more than 5% ownership.

Designated officials at the investigator's institution must review the disclosures, and if they determine that a conflict could affect the research, the institution must report it to the NIH and act to protect the research from bias.[2] Similar regulations exist for projects regulated by the US Food and Drug Administration (FDA).[3]

Ethical dilemmas are compounded when investigators are also study sponsors. In the case of *Gelsinger v University of Pennsylvania*,[4] an 18-year-old research subject died during a gene transfer experiment for ornithine transcarbamylase deficiency. The principal investigator, a physician, founded the company that was sponsoring the trial and owned as much as 30% of the company's stock. The University of Pennsylvania also owned 5% of the company's stock.

The Center for Science in the Public Interest argues that disclosure of financial ties and other potential sources of bias is an

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important mechanism of accountability. They sponsor an online database of investigators' financial ties to sponsors (http://www.cspinet.org/integrity/). The information is indexed according to hospital, university, physician, and investigator.

Conflict of dual role of physician-investigator

An innate conflict also exists when one person is both physician and clinical investigator, especially when subjects are drawn from the physician's own pool of patients.[5] In this situation the physician assumes the dual role of both caring for patients and performing research on them, two functions that may conflict. Several ethical issues may arise as a result of outlooks of both the physician and the patient.

Coercion to enroll or stay in a study. One danger is that a physician may aggressively recruit research subjects to the point of coercion and may not fully inform patients of the study's risks or other treatment options. The potential for a problem is especially great when the sponsors of a study offer financial bonuses to investigators for rapid enrollment.

In the case of *Guckin v Nagle*,[6] a surgeon who also functioned as a clinical investigator recommended an experimental intervention as "the best therapeutic alternative" for a patient's occasional fecal incontinence. The patient's anal sphincter was permanently damaged when the radiofrequency device overheated and failed to shut off automatically. The consent form did not indicate that the procedure was part of a clinical trial, nor did it mention alternative treatments. The patient argued that she was a victim of "therapeutic misconception," that is, she believed that the intervention would directly benefit her based on the information provided by the surgeon and the consent form.

In the case of adverse events occurring during a study, a physician-investigator may be tempted to choose an intervention that keeps the individual enrolled rather than one that is clinically the most appropriate.

Patient confusion about the dual role. A patient may feel obliged to enroll in a study to "help" his or her doctor in return for the care the doctor provides. Patients may also feel that the doctor would not be offering study participation unless it were safe or to their benefit.

Patients are especially vulnerable when they are desperate for treatment or if they lack health insurance. In such cases they may seek out research studies as a form of health care.

Full disclosure recommended

Some of these dilemmas may be avoidable, but others are not. The best approach is for the clinician-investigator to explicitly disclose any dual interest. This can be done by including the following in the protocol's consent form and verbally reviewing it with prospective research subjects:

"Your doctor may be an investigator in this research study. Because of this, he or she is interested in both your welfare and in the conduct of this study. Before entering this study or at any time, you may ask for a second opinion about your care from another doctor who is not part of the study. You are not required to participate in any research offered by your doctor."

Research subject advocates

In cases in which conflict of interest is significant and unavoidable, it may be appropriate to use a research subject advocate.[7] Some research centers employ an advocate (often a doctoral-level nurse with training in research ethics or a bioethicist) to assist with the consent process as a witness or to help answer questions posed by subjects about study design, risks and benefits, and rights.

Advocates might also help if clinical investigators are pressed for time or if their participation in the consent process might be viewed as coercive. Advocates can be instrumental in research ethics education: they can help clinician-investigators recognize conflicts of interest and assist in creating appropriate consent forms.

When sponsors offer bonuses for rapid enrollment, the potential for coercion exists

CREATING CONSENT FORMS

Consent forms can be difficult documents to create for a number of reasons.

The form must be understandable. Explaining complex procedures at the recom-

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TABLE 2

Simplifying language in consent forms

INSTEAD OF...	SAY...
Altered mental status	Confused
Assay	Test
Bradycardia	Slow heart rate
Dyspnea	Shortness of breath
Pruritus	Itching
Syncope	Fainting
Tachycardia	Fast heart rate

TABLE 3

Avoiding misleading terms in consent forms

ETHICALLY APPROPRIATE	ETHICALLY INAPPROPRIATE
Investigator, researcher	Doctor, physician
Research, study, investigation, project, experiment	Medical/surgical treatment, health care
Drug, device, intervention	Medicine, medication, therapy, treatment, remedy, cure
Research subject, research participant	Patient

mended eighth-grade reading level can be a challenge (TABLE 2).[8] In some cases, the consent process may need to be tailored to the comprehension level of the enrolling subjects, and additional tools such as videos, comic books, and brochures may assist this process.[9–11]

Further, investigators should be cautioned that exceedingly lengthy and complex consent forms can deter research subjects from reading them.

The form must not be coercive. Potentially persuasive terms should be avoided (TABLE 3). "Study medicine" and "study medication" imply therapy or benefit: it is more appropriate to use the word "drug," a more neutral term. Similarly, "physician" and "doctor" convey an expectation of care and treatment rather than experimentation; thus, "researcher" and "investigator" are more appropriate. In addition, the words "study," "research," "experiment," and "investigation" should be used frequently as a reminder that the intervention is not standard medical care, but research for the benefit of future patients.

The form must stand up in court. Consent forms are often used as evidence in litigation, so great care must be taken in their wording.

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