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Just Sign on the Dotted Line?

Unsettled legal questions complicate obtaining subjects' consent to medical research.

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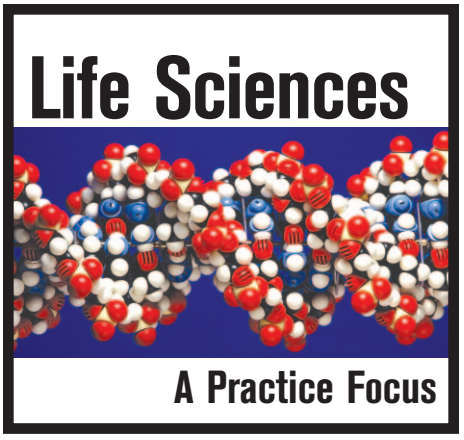
Medical research studies with human subjects are essential to develop lifesaving drugs and medical devices. The medical community needs volunteers—both healthy individuals and those with the disease or condition being investigated—for such studies. The subject's informed consent is key to ensuring that participation is voluntary.

Government regulations set forth requirements for obtaining informed consent to enroll in medical research. But the regulations don't specifically address everything, leaving unsettled areas that complicate the researcher's duty to ensure that volunteers receive complete information.

Regulating Consent

Along with review of the study by an independent committee or institutional review board, each individual's voluntary and informed consent to participate forms the cornerstone of the protection of the rights and welfare of human subjects.



In the United States, informed consent is governed by the Federal Policy for the Protection of Human Subjects (also known as the Common Rule), a set of regulations adopted by 17 federal agencies in June 1991. The Food and Drug Administration has its own regulations, which share the core principles of the Common Rule. The Common Rule applies to studies funded or conducted by federal agencies. The FDA regulations apply to studies of FDA-regulated products, such as drugs, biologics, and medical devices.

The FDA regulations lay out the basic requirements for informed consent. Volunteers must be told, among other disclosures, that the study involves research, the purpose and duration of the study, reasonably foreseeable risks and discomforts to the subject, alternatives to participation, the extent to which confidentiality will be maintained, whether any compensation will be provided, what will happen if the subject is injured or becomes ill, and the names of individuals to contact with questions about the study or the subject's rights. Informed consent may not include exculpatory language, under which a study subject would appear to waive any legal right, and generally must be obtained in writing.

Applying these seemingly simple requirements can be quite complicated in practice. Three areas that present recurring issues are disclosure of conflicts of interests, use of "banked" tissue samples, and genetic testing.

Conflicts of Interest

Clinical studies are typically conducted by physicians who perform the research for a particular company that sponsors the research. Neither the FDA regulations nor the Common Rule addresses the need to disclose to subjects the investigators' potential conflicts of interest. The question of when possible conflicts should be disclosed to subjects, though, is getting increasing attention.

The financial arrangements between clinical investigators and the sponsor of the study can vary widely. Investigators are generally compensated for the costs associated with each subject enrolled in the study. Such payments to reimburse the investigator for direct expenses, overhead, and staff time spent on the research should not trigger the need for disclosure to subjects. But other arrangements may be more problematic.

Investigators may be paid a sum that substantially exceeds the costs of performing the study, effectively turning the investigation into a profit center. Sponsors sometimes offer financial bonuses to investigators if they enroll a specified

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number of subjects or meet a deadline for subject accrual. Investigators may have other ties to the sponsor, such as serving as consultants. Alternatively, investigators may have received stock for past services; this can be of particular concern if the company is privately held. Less frequently, the investigator may also be the inventor and thus have a financial stake in the success of the product being studied, such as patent rights or royalties.

Although the FDA's informed consent regulations do not expressly address conflicts, the FDA has issued other regulations that require disclosure of certain financial arrangements to the agency. Specifically, the FDA requires that sponsors disclose in their marketing applications whether investigators have received payments with a monetary value of more than $25,000 (excluding the costs of conducting the study) or have a significant financial interest in the sponsor, meaning an equity interest of more than $50,000 in a publicly traded company.

The FDA has stated that it needs this information to determine whether bias may have affected the research data. Sponsors should consider under what circumstances—if any—a mandatory disclosure to the FDA may also trigger the need to notify subjects.

Historically, there was little civil litigation involving clinical studies. That has changed in the past few years. One potential theory for plaintiffs is that consent without disclosure of conflicts is not adequate and meaningful. A subject injured during a clinical study may argue that if the financial arrangement between investigator and sponsor was significant enough to trigger disclosure to the FDA, the subject should also have been told about it before deciding whether to participate.

Few courts have directly considered this issue. In *Moore v. Regents of the University of California* (1990), the plaintiff alleged that he had not been told of his physicians' financial stake in the cell line developed from his spleen. The California Supreme Court allowed this claim to proceed, holding that a physician has a duty to disclose personal research or commercial interests unrelated to the patient's health that may affect the physician's professional judgment. The court expressed the concern that when a physician brings his own economic or research-related interests to the decision of how to treat a patient, he may be "tempted to order a scientifically useful test or procedure that offers marginal, or no, benefits to the patient."

In *Greenberg v. Miami Children's Hospital* (2003), the U.S. District Court for the Southern District of Florida distinguished *Moore*. In *Moore,* the physician had a therapeutic relationship with the patient. In *Greenberg,* the defendants were medical researchers only and had no therapeutic relationship with the study subjects. The court declined to extend the duty of informed consent under state law to include economic interests in the medical research setting.

In the widely publicized case of the teenager who died in 1999 while participating in a gene-transfer study, the plaintiffs in *Gelsinger v. Trustees of the University of Pennsylvania* alleged that researchers failed to disclose a conflict of interest in the form of ownership of the sponsoring company. The case was ultimately settled.

While the legal standards for when subjects should be told about the financial relationship between investigators and sponsors are ill-defined, sponsors, investigators, and institutional review boards should consider this potential issue when drafting consent forms.

Banked Specimens

Informed consent is generally required before an individual can participate in a clinical study that will support the regulatory approval of a drug, device, or biologic. The situation is different if investigators want to study cells or tissue that was previously collected, especially if investigators have no way of knowing whose biological material is being tested.

FDA regulations generally require that a human subject provide informed consent. The term "human subject" is defined in the regulations as "an individual who becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient."

The term "participant" is not defined by the FDA. It is not clear how a patient can become a participant through a specimen that is sent to a laboratory for analysis if that specimen has been stripped of all identifiers and cannot be traced back to the patient. Under these circumstances, obtaining consent is neither practicable nor necessary to protect the patient.

After all, the patients whose specimens are tested face no health risks from these tests, and their privacy rights are not jeopardized. The situation is different if patient identity is known or patient records need to be reviewed, but that represents a minority of cases in which banked specimens are used.

Nevertheless, at least some individuals at the FDA have asserted in speeches and discussions with industry that informed consent is required for these banked, "anonymized" specimens.

This viewpoint has created controversy and uncertainty, particularly within the in vitro diagnostic industry. That industry depends on access to stored specimens to develop, test, and refine its diagnostic tests. Using only specimens for which informed consent has been given would dramatically slow in vitro innovations. Retrospectively getting consent from patients whose cells were removed by their physician for medical tests would be a huge burden—or impossible.

The FDA has stated that the questions concerning the use of "residual" specimens are "complex." But the agency has let this complexity languish for too long, and the uncertainty is hampering research. Finally and explicitly, the FDA needs to declare that informed consent is not needed when banked, anonymized specimens are used by companies to develop or test in vitro diagnostic products.

Genetic Testing

Genetic testing is also playing a more important role in the development and approval of FDA-regulated products. Pharmacogenetics and pharmacogenomics (that is, the use of genetic variations that may correlate with pharmacologic function and therapeutic response in conjunction with drug therapy selection) are becoming increasingly important.

While federal regulations do not specifically address the additional concerns in obtaining consent for studies that involve genetic testing, many states have laws that address genetic testing, particularly with regard to the confidentiality of the results of these tests. The FDA's informed consent regulations do not pre-empt state laws. Although medical researchers tend to look to federal law to govern most aspects of clinical research, adherence to pertinent state and local laws is critical. Still, there are significant ambiguities in determining what constitutes adequate

disclosure to subjects asked to participate in studies that involve genetic testing.

The FDA's general requirements for all studies, genetic or otherwise, must be satisfied. Its informed consent regulations state, for example, that reasonably foreseeable risks must be disclosed and that subjects must be informed of how confidentiality will be maintained.

Regarding risks that should be disclosed to the subject, in addition to any physical discomfort, there may be certain "nonphysical" harms to consider. For instance, an investigator must consider to what extent the subject's psychological well-being may be harmed if the subject is informed of the genetic test results. Indeed, it may be that the subject should have the right to decide whether to be informed. Individuals vary in their desire to know the results of genetic testing, particularly if a genetic predisposition may be uncovered for a disease for which there is no effective treatment.

In the case of genetic testing, maintaining confidentiality and nondisclosure of results to third parties is particularly important. Those diagnosed with a particular genetic makeup or disorder risk discrimination by employers, fellow workers, and health insurance providers.

Another complication that the investigator must address is how and whether to inform the subject's family members, who may or may not also want to be tested. Indeed, this dilemma raises the question of who is the subject in research involving genetic testing. While not considered study participants within the meaning of the regulations, entire families may be affected by one person's decision to participate and the knowledge that individual acquires about his or her genetic composition.

Voluntary and informed consent to participate in medical research is key to the protection of the rights and welfare of human subjects. The FDA's regulations adequately address many common issues. Sponsors and investigators, however, will find insufficient guidance when dealing with some very important questions.

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