
Informed Consent in Clinical Trials of in Vitro Diagnostic Devices: Perspectives from the FDA and Manufacturers

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Editor's Note: In view of current controversies in the US about informed consent for clinical studies of in vitro diagnostic devices, Associate Editor Fred Apple invited perspectives from the FDA and from two clinical scientists who work for manufacturers. The perspectives were peer-reviewed, revised, edited, and appear here. They add clarity to a topic that affects not only clinical chemists in industry and hospitals, but also the public health and public trust. DEB.

A Perspective from the Food and Drug Administration

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The need for informed consent from human subjects whose specimens are used in in vitro diagnostic studies is sometimes questioned. This is especially the case if the research carries only minimal risk to the subject. However, the process of obtaining informed consent recognizes the autonomy of the human subject to decide whether to participate in research regardless of whether there are risks. In this opinion, we will discuss the history of ethics in medical research and how this relates to federal regulations governing informed consent (see Table 1).

Human participants in biomedical research contribute tremendously to our overall societal good. Unfortunately, the history of medical research is checkered with several unethical studies. For example, past atrocities, such as those described at the Doctor's Trial at Nuremberg, Germany (1) and in the syphilis study at Tuskegee, Alabama (2), showed no respect for the autonomy of human research participants. These and other unethical studies have influenced the rules governing modern biomedical research.

The basic principles underlying the current US federal regulations for human biomedical research can be traced to three landmark documents. The first document was the Nuremberg Code (3), formulated for the Doctor's Trial at Nuremberg in 1947 and later adopted by the American Medical Association. The first of the 10 principles of the Nuremberg Code is "The voluntary consent of the human subject is absolutely essential". Although the entire Nuremberg Code has not been formally adopted as law by any nation, its basic requirement for informed consent is a universal standard expressed in both international law (4) and international ethical guidelines for conducting human biomedical research (5). This document is often cited as the most important in the history of the ethics of medical research.

The second salient document is the Declaration of Helsinki, which was promulgated by the World Medical Association in 1964 and has since undergone several revisions, most recently in 2000 (6). One of the basic principles stated in all versions of the Declaration of Helsinki is that the right of the research participant to safeguard his or her integrity must always be respected. It also states that concern for the interests of the subject must always prevail over the interest of science and society.

The third document considered a cornerstone in the ethical conduct of biomedical research is the Belmont Report (7). Of the three basic principles in the Belmont Report, respect for persons and their function as autonomous agents is paramount and demands that subjects enter into the research voluntarily and with adequate information.

The Federal Policy for the Protection of Human Subjects, often termed the "Common Rule", refers to Subpart

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Table 1. FDA law and regulations addressing informed consent.

Law: Federal Food, Drug, and Cosmetic Act

Section 520(g)(3)(A)–IRB Review

Section 520(g)(3)(D)–Informed Consent

Regulations: Code of Federal Regulations

21 CFR 50–Informed consent

21 CFR 50.23 and 50.24–Criteria for Waiver

21 CFR 56–IRB review

21 CFR 56.104 and 56.105–Conditions for Exemption

21 CFR 812–IDE regulation

21 CFR 812.2(c)(3)–Conditions for IVD Exemption

A of 45 Code of Federal Regulations (CFR) Part 46 (8). In 45 CFR 46.102(f), the Common Rule defines a human subject as “a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information”. On the basis of this definition, specific criteria for waiver of informed consent or Institutional Review Board (IRB) review are laid out in 45 CFR 46.116(d). Regulations applicable to Food and Drug Administration (FDA)-regulated products in general, and to in vitro diagnostics in particular, differ from the Common Rule in very specific ways with regard to the definition of a human subject, as well as the criteria for waiver of informed consent or IRB review (see below).

Section 520(g) of the Federal Food, Drug, and Cosmetic Act (the Act) provides the statutory requirements for investigations of medical devices (9). The requirements for obtaining IRB review and informed consent are contained in sections 520(g)(3)(A) and 520(g)(3)(D), respectively. The Act requires that IRB review and informed consent are obtained for all clinical investigations of medical devices, and the only exception provided for in the Act is a life-threatening situation.

How the FDA implements these sections of the Act can be found in three regulations, 21 CFR Parts 50, 56, and 812. Part 50 is the regulation pertaining to protection of human research participants and includes the FDA requirements for informed consent of human participants (10). The scope of this regulation (section 50.1) states that “this part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration. . . .” Section 50.20 states that “Except as provided in sections 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative”. Sections 50.23 and 50.24 address exceptions from informed consent in life-threatening situations. Therefore, the regulations are

consistent with the statute in requiring informed consent of all human research participants except in life-threatening situations. Part 56 is the regulation pertaining to IRB review (11), with sections 56.104 and 56.105 addressing the exemptions from, or waiver of IRB requirements.

The investigational device exemptions regulation is found in 21 CFR 812 (12). Under section 812.3(p), the definition for subject states that “Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease”. This definition clearly identifies the FDA’s intent to include “specimens” when identifying subjects of investigations of medical devices. Sponsors of many in vitro diagnostic products may be exempt from following the investigational device exemptions (IDE) regulation based on the exceptions listed under section 812.2(c)(3). The exceptions, all of which must be met to enable exemption, are that the in vitro diagnostic device (IVD) (a) is properly labeled as investigational, (b) is noninvasive, (c) does not require an invasive sampling procedure that presents significant risk, (d) does not by design or intention introduce energy into a subject, and (e) is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure. However, sponsors of in vitro diagnostics are not exempt from the requirements for obtaining IRB review and informed consent found in 21 CFR 56 and 50, respectively. This is also spelled out in the FDA guidance document entitled, “Regulating In Vitro Diagnostic Device (IVD) Studies”, issued December 17, 1999 (13). As discussed in the guidance, the use of biological materials that are traceable to a specific person constitutes human-subjects research and therefore requires IRB review and informed consent. If, however, samples used in a study are not traceable to a specific individual, the informed consent rules would not be applicable.

The National Bioethics Advisory Commission (NBAC) has recommended some ways to clarify the definition of human-subjects research under the Common Rule (14). Interestingly, NBAC’s recommendation 1(c), which states that research conducted with coded or identified samples is research on human subjects, is quite consistent with the statement in the FDA IVD guidance document. Another statement in the NBAC document that is particularly pertinent to research using leftover or retrospective samples, as is often the case for IVD studies, comes in recommendation 8. They indicate that simply because an individual may have signed a consent form for one kind of research, it cannot be assumed that the consent is applicable to all types of research for an indefinite period of time. Recommendation 9 of this same document gives examples of some of the options that might be considered in developing future consent forms to allow individuals increased autonomy in determining the use of their biological samples in future research. At the same time, it decreases the burden of having

to go back to individuals to obtain a new consent each time their samples are used in evaluating a new IVD.

The differences between the Common Rule, applicable to Department of Health and Human Services (DHHS)-funded research, and FDA regulations, applicable to FDA-regulated products, can be a source of confusion for an investigator. For clarification, it should be pointed out that if biomedical research is conducted with the intent to support a marketing application to the FDA, the FDA regulations must be followed. Additionally, if the DHHS-funded research is also on FDA-regulated products, the most stringent of the applicable regulations for each aspect of the study must be followed. The informed consent document also notifies individuals of the possibility that their records may undergo review by the FDA. This notification respects a subject's autonomy by informing him or her that FDA has the right to audit/review patients' medical records if deemed necessary to support a marketing application.

There are three principles underlying ethical biomedical research: respect for autonomy, beneficence, and justice. Respect for autonomy is the principle specifically expressed through an individual's consent or refusal to participate in a particular research activity. Respect for autonomy dictates that individuals are allowed to make this decision whether it involves their bodies in toto or use of their biological material. The FDA regulations and guidance require IRB review of in vitro diagnostic studies and informed consent from the participants. The FDA recognizes that there may be some ambiguity in the interpretation of the informed consent policy and is working toward an equitable resolution of this issue.

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A Perspective from Manufacturers

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The conduct of clinical investigations for biologics, drugs, and devices shares many common elements, regardless of the center with the Food and Drug Administration (FDA)

that ultimately reviews the study results. The roots for this commonality can be found in the Food, Drug, and Cosmetic Act. Generally, investigations conducted by sponsors conform to the elements of good clinical practice (GCP), such as informed consent (1), Institutional Review Board (IRB) review (2), financial disclosure (3), and the filing of study plans and required documentation before clinical evaluation of an investigational product [Investigational Device Exemption (IDE) for devices, and Investigational New Drug (IND) application for drugs and biologics] (4, 5).

In vitro diagnostic (IVD) devices are a subset of devices and are defined as “those reagents, instruments, and systems intended for use in the diagnosis of disease or

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other condition, including a determination of the state of health, to cure, mitigate, treat, or prevent disease or its sequelae. Such products are usually intended for use in the collection, preparation and examination of specimens taken from the human body" (6). Because testing does not usually require invasive sampling that presents a significant risk and because the result of the investigational test is not used in the clinical management of patients, IVDs are usually exempt from the requirements for IDE filing before the start of a study. IVD investigations are usually subject to IRB review, but may or may not be exempt from informed consent requirements; this depends on the device and the purpose and nature of the study.

The FDA classifies devices (including IVDs) into one of three regulatory classes: Class I, II, or III (7). The FDA classification of a device is determined by the amount of regulation necessary to provide a reasonable assurance of safety and effectiveness. Class III is typically reserved for the highest risk devices, which require the greatest amount of information to ensure safety and effectiveness; these usually require a Pre-Market Approval Application (PMA). Conversely, most Class I or II IVDs present minimal risk to patients and do not require extensive patient data.

In December 1999, the FDA issued a Staff Guidance document "Regulating In Vitro Diagnostic Device Studies" (8). The document clarified the agency's position on interpretation and enforcement of existing regulations guiding IVD investigational studies. Most notably, the agency asserted the importance of patient confidentiality by emphasizing the need for both IRB review and patient informed consent for any study using leftover biological material, such as blood samples, that can be traced back to the donor (linked) by a patient identification number or code.

IVD manufacturers agree with the agency's position regarding a patient's right to privacy. Specifically, for Class III (and some Class II) studies, the extensive patient data required for filing necessitates the need for both sponsor and agency review of patient records for accuracy, and informed consent is appropriate for these studies. Consent requirements for well-characterized Class III products not involving extensive patient data could be discussed with the FDA before study initiation.

At issue is informed consent for lower-risk devices requiring limited patient data. For most Class I or Class II device studies, IVD manufacturers traditionally work directly with the laboratory, and not a clinician, to obtain desired samples. Because serum, plasma, or other biological fluids can be stored appropriately for periods of time, laboratory study personnel can store specimens while awaiting results from a predicate device (existing, legally marketed device) or search for patients with certain characteristics, according to the study design. Samples can also be collected independent of a specific protocol and stored for extended periods (banked) until required by a specific study design. Clinical evaluation of these

Class I or Class II devices generally consists of establishing assay performance characteristics (e.g., imprecision) and equivalence to a predicate device with method-comparison studies. If patient information is required, it is typically limited to demographic data such as age and sex. Such retrospective studies limit sample size and cost while providing the required analytic and clinical information for agency review.

For these studies, informed consent is usually waived by the institution's IRB after assessing patient risk. The Principal Investigator maintains the privacy of patients by restricting sponsor access to patient records and by use of patient identification numbers to identify relevant clinical or demographic information and transmit data. The patient remains anonymous to the study sponsor. Because the majority of IVDs used in laboratories are minimal risk Class I or Class II devices, this approach is widely practiced.

The December 1999 FDA document affects this process in two ways. (a) The agency maintains that coded samples may not adequately protect an individual's privacy because the codes can be traced to a particular patient (by the study Principal Investigator or the institution). (b) Some in the agency assert that without informed consent, they are unable to review patient records for accuracy and compliance purposes if necessary. Therefore, informed consent would be required. This newly explicit description of the agency's approach to informed consent raises several concerns regarding the future feasibility of conducting studies of low-risk devices. These concerns should be considered and discussed to develop a system that would allow the development of new tests and also protect patient confidentiality.

The current practice, and its success in providing valid scientific data while maintaining patient confidentiality, relies on the waiving of signed informed consent requirements by an institution's IRB for these minimal risk studies. Requiring informed consent will change a sponsor's ability to conduct these studies, both in frequency and scope. Informed consent will require additional personnel to obtain informed consent from patients, manage documents, and audit a site's compliance. This will increase the cost of the studies and prolong time to market because of slower subject recruitment and more stringent administrative requirements. These effects will have a negative impact on discovery research, technology development, and product enhancements and will discourage clinical exploration for new assay indications. Finally, it has the potential to change the face of the marketplace by decreasing competition as manufacturers, large and small, find it difficult to justify the investment required for clinical studies.

The effects will go beyond IVD manufacturers. Fewer laboratories will have the personnel and infrastructure to support informed consent requirements for even the smallest of studies. The increased expense of conducting studies will drive up the cost of new tests for laboratories,

patients, and the healthcare system as a whole. Decreased competition and testing options will also drive up costs. Fewer new tests or incremental improvements to existing tests will negatively impact the advancement of medical care.

Resolution of this situation is made more difficult by several other initiatives, at state and national levels, addressing privacy protection of human research subjects. Most notably, The Health Insurance Portability and Accountability Act (HIPAA) and the National Bioethics Advisory Commission's report on research involving human biological materials also address related issues, including concerns about patient informed consent, an IRB's role in reviewing and monitoring clinical research, and deidentifying patient data before transmission (9, 10). These efforts are rooted in concerns about genetics research, but their implications extend to all human research investigations. These issues are complex, and it is critical that clear guidance be provided to IRBs, laboratories, and sponsors of IVD studies. Clear understanding is needed to maintain the ability of biomedical researchers to provide striking new diagnostic tools for improving human healthcare.

In summary, many IVD manufacturers feel that most Class I and II studies should be considered for exemption from informed consent requirements to balance the concerns of patient privacy and advancement of medical care. Specifically, those studies that do not require the patient to undergo any additional medical procedures expressly for the study, do not use the result of the investigational test in patient management, present no risk to the patient, and collect only limited data that are then coded and sent to the study sponsor should be considered for exemption. The collection of limited data, such as age, sex, or analyte concentration, does not provide enough information to personally identify an individual patient.

For Class III (and some Class II) studies that involve extensive patient data, informed consent would be required. Future discussions among all parties interested in

the protection of patient privacy should further define the requirements for studies in the gray area between these two extremes and for well-characterized Class III devices, allowing manufacturers to plan their research studies appropriately and to continue providing important advancements in the diagnosis and management of disease.

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