

Challenges in Human Subject Protection

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I. INTRODUCTION

This article presents for consideration several difficult human subject protection issues currently confronting the Food and Drug Administration (FDA). These matters pose a challenge not only to the agency, but also to institutional review boards (IRBs), clinical investigators, sponsors, and legal advisors.

Before defining these issues, this article provides a quick overview — in the broadest terms — of some of the FDA's human subject protection regulations. This overview will be useful in providing the context necessary to understand the challenges to be discussed.

II. REVIEW OF FDA REGULATIONS

The FDA's regulations pertaining to IRBs are found in part 56, title 21 of the *Code of Federal Regulations*.¹ Part 56 sets forth the general standards for the composition, operation, and responsibility of an IRB. As expressly stated in part 56, "Compliance with this part is intended to protect the rights and welfare of human subjects involved in [clinical] investigations."² The regulations fundamentally are *process* regulations; they prescribe the process that should govern the functioning of an IRB and the criteria that an IRB should apply in deliberations. The regulations do not provide answers to the many difficult questions, which often are questions of judgment, that an IRB is required to resolve.

The most salient requirements of part 56 are:

- An IRB must be comprised of at least five persons of various backgrounds whose experience, expertise, and diversity will "promote respect for its advice and counsel in safeguarding human subjects."³ At least one member must be unaffiliated with the institution sponsoring the IRB, and one member must be a person whose primary "concerns" are nonscientific in nature.⁴
- The IRB is responsible for evaluating the research protocol, which defines the purpose of the research and the means by which it will be carried out.⁵ In addition, the IRB must review the informed consent document provided to each research subject.⁶ In performing this review, the IRB must ensure that the informed consent

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¹ 21 C.F.R. pt. 56 (1995).

² *Id.* § 56.101(a).

³ *Id.* § 56.107(a).

⁴ *Id.* § 56.107(c), (d).

⁵ *Id.* § 56.109(a).

⁶ *Id.* § 56.109(b), (c).

document contains all of the factors delineated in the regulations.⁷ Evaluation of the consent form involves an assessment of its completeness in light of the risks of the study, and its comprehensibility from the perspective of the entire range of subjects who may be accrued.

- In reviewing the protocol, the IRB is required to ensure that subject selection is “equitable,” taking into account the purpose of the research and the setting in which it will be conducted.⁸
- A study protocol may be approved only on a determination that risks to subjects have been minimized,⁹ the research design is sound,¹⁰ and the risks to subjects is “reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may be expected to result.”¹¹
- The IRB has continuing responsibility during the course of a clinical trial to evaluate whether any new information that may have emerged during the course of the study necessitates modification of the consent form, changes in the protocol, or termination of the study.¹²
- Finally, if an IRB determines that research is not being conducted in accordance with the approved protocol, or that there has been “unexpected serious harm to subjects,” the IRB may suspend or terminate its approval. Such action must be reported promptly to the investigator, appropriate institutional officials, and the FDA.¹³

Closely related to the IRB regulations are the FDA’s regulations governing informed consent, located at part 50, title 21 of the *Code of Federal Regulations*.¹⁴ The requirements of the informed consent regulations generally are more specific than the IRB regulations; for example, they prescribe specific information and types of information that must be imparted to research subjects.¹⁵

The fundamental precept regarding informed consent is clear: “[N]o investigator may involve a human being as a subject in research . . . unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative.”¹⁶ The only exceptions are certain emergency situations.¹⁷

A brief summary of the informed consent regulations includes the following points:

- The circumstances under which informed consent is obtained must not be coercive.¹⁸
- The information provided to the subject must be in language that is understandable to the subject or the representative.¹⁹
- No informed consent may include “exculpatory language” or include language that

⁷ See *id.* §§ 50.20, 50.25.

⁸ *Id.* § 56.111(a)(3).

⁹ *Id.* § 56.111(a)(1).

¹⁰ *Id.* § 56.111(a)(1)(i).

¹¹ *Id.* § 56.111(a)(2).

¹² *Id.* § 56.109.

¹³ *Id.* § 56.113.

¹⁴ *Id.* pt. 50.

¹⁵ *Id.* § 50.25. The actual wording, however, is left to the IRB.

¹⁶ *Id.* § 50.20.

¹⁷ See *infra* section III, subhead A, for a discussion of these exceptions.

¹⁸ 21 C.F.R. § 50.20.

¹⁹ *Id.*

- suggests that the subject has waived any legal rights.²⁰
- Subjects must understand that they are being asked to participate in research,²¹ that their participation is voluntary,²² and that they may withdraw at any time.²³ Additionally, the potential risks²⁴ and benefits²⁵ of their participation must be adequately disclosed, together with information about alternate treatments²⁶ that may be available.

Note that this is not a complete list of all of the elements found in the informed consent regulations.

Although not expressly stated in part 56 of the regulations, the FDA's IRB regulations do not preclude IRBs from imposing standards that are higher than prescribed in the regulations. In the preamble to the final rule, the FDA stated:

An institution or IRB is free to impose greater standards of protection for human subjects than those required by these regulations [The] FDA does not believe that it should provide detailed directions to IRBs on how they are to comply with these regulations. How the IRBs meet the general standards should be left to each individual IRB and institution.

III. NEW CHALLENGES

The human subject protection challenges facing the FDA may be divided into two broad categories: legal/regulatory/ethical challenges and challenges pertaining to understanding and complying with the FDA's regulations (or "comprehension challenges").

A. *Legal/Regulatory/Ethical Challenges*

Turning first to the legal/regulatory/ethical challenges, three issues have been the subject of much recent discussion and debate. These issues are:

- informed consent in emergency research,
- the use of placebo controls in certain studies, and
- the current relevance of certain documents that have been the ethical touchstone for research in human subjects for several decades.

1. *Informed Consent in Emergency Research*

Over the past several years a number of studies, involving both drugs and devices, have confronted the FDA with study designs that call for the test article to be administered to an unconscious or otherwise incapacitated patient. One of these studies, the PEG-SOD study, involved a drug aimed at limiting neurological damage following head trauma. Another study concerned the "Ambu Cardiopump." This device was being investigated for use in cardiopulmonary resuscitation, a situation that usually does not lend itself to prior informed consent.

²⁰ *Id.*

²¹ *Id.* § 50.25(1).

²² *Id.* § 50.25(8).

²³ *Id.*

²⁴ *Id.* § 50.25(2).

²⁵ *Id.* § 50.25(3).

²⁶ *Id.* § 50.25(4).

The permitted exceptions to the informed consent regulations have changed over the history of the statute. Depending on whether the investigational article is a drug or a device, the Federal Food, Drug, and Cosmetic Act (FDCA) prescribes different standards for an exception.²⁷ The 1962 amendments to the FDCA included the requirement that subjects participating in clinical trials be provided with informed consent. The language of these Amendments — still extant in the statute²⁸ — permits an exception to the informed consent requirement based solely on a physician's determination that providing informed consent is either "not feasible" or is "contrary to the best interest" of the patient. In January 1963, the FDA implemented this statutory language in regulations that gave responsibility for protecting patients' rights to the clinical investigator, without substantial limitation.²⁹

The 1976 Medical Device Amendments (MDA) to the Act set a stricter standard for the study of investigational devices in subjects unable to provide informed consent.³⁰ The 1976 device amendments added to the requisite of "nonfeasibility" a requirement that the patient be faced with a "life-threatening" situation. Moreover, under the MDA the possible benefits of using the device must support a conclusion that the situation "necessitates the use" of the device.

Why is there a stricter standard for devices? The answer has nothing to do with inherent differences between drugs and devices; rather, the discrepancy stems from two events that intervened between 1962 and 1976. First, several stunning revelations raised serious questions about the wisdom of delegating broad, unilateral discretion in this area to investigators. The most well-known of these revelations appeared in the Public Health Service (PHS)-funded Tuskegee Study³¹ and the studies described in a 1966 *New England Journal of Medicine* article by Dr. Harry Beecher.³² Second, in 1974 Congress enacted the National Research Act,³³ which mandated the creation of a National Commission to provide recommendations on informed consent. The best-known of the Commission's reports was the *Belmont Report*.³⁴ This report articulated three basic principles of human subject protection that must govern clinical research: respect for the autonomy of each research subject, beneficent treatment of subjects, and justice in allocating benefits and burdens of research.

In 1981, the FDA promulgated its IRB and informed consent regulations. The agency extended the stricter informed consent exemption derived from the MDA to all regulated products, including drugs. The FDA's current informed consent regulations contain four criteria that are needed to invoke an exception:

- The subject must be confronted by a life-threatening situation that necessitates the use of the investigational drug or device;³⁵

²⁷ Pub. L. No. 75-717, §§ 505(i), 520(g)(3)(D), 520 Stat. 1040 (1938) as amended 21 U.S.C. §§ 355(I), 360j(g)(3)(D) (1993).

²⁸ See FDCA, § 505(i), 21 U.S.C. § 355(i).

²⁹ See Pub. L. No. 87-781, 76 Stat. 780 (1962).

³⁰ See FDCA § 520(g)(3)(D), 21 U.S.C. § 360j(g)(3)(D).

³¹ See Jean Heller, *Syphilis Victims in U.S. Study Went Untreated for 40 Years*, N.Y. TIMES, July 26, 1972, at 1,8.

³² Harry Beecher, *Ethics in Clinical Research*, 274 NEW ENG. J. MED. 1354 (1966).

³³ Pub. L. No. 93-348, 88 Stat. 342 (1974).

³⁴ NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH, DHEW Pub. No. (OS) 78-0012 (1978).

³⁵ 21 C.F.R. § 50.23(a)(1).

- Informed consent cannot be obtained from the subject because of the subject's inability to communicate or give legally effective consent;³⁶
- Time is not sufficient to obtain consent from the subject's legal representative³⁷ (the FDA defers to state law on the question of who may be a "legal representative"³⁸); and
- There is no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.³⁹

In addition, both the investigator and a physician not participating in the investigation must certify in writing that all of the above conditions exist.⁴⁰ If time does not permit the involvement of an independent physician, then review by such a physician must be obtained within five days following the article's use.⁴¹

While most would agree that the stricter requirements have been fairly effective in discouraging unwarranted or cavalier circumvention of the informed consent requirement, it is also widely held that the FDA's current regulations pose a barrier to the conduct of certain types of research. Moreover, much important research occurs at hospitals having "multiple project assurances" with the Department of Health and Human Services (DHHS), so investigators must comply with both DHHS and FDA requirements. In contrast to FDA regulations, DHHS regulations permit a waiver of informed consent only when the research involves "no more than minimal risk to the patients."⁴² Some have concluded that "minimal risk" in this context refers only to the increment of risk faced by administering the investigational product to the research subject; if the patient is already *in extremis*, even the fairly significant risks associated with an investigational product may be deemed acceptable. The examples of minimal risk found in the DHHS regulation, however, suggest that the drafters intended the term "minimal risk" to encompass only the most benign interventions.⁴³

To explore these issues more fully, the FDA and the National Institutes of Health (NIH) cosponsored a public forum on the ethical and practical problems of informed consent in emergency research.⁴⁴ Over 300 people attended the meeting, including leading emergency medicine researchers and biomedical ethics experts. Invited speakers presented the historical background and legal requirements currently governing emergency research; several case studies exemplifying some difficult issues in this context were analyzed and discussed.

Almost all of the speakers at the joint FDA/NIH meeting agreed that this important research should be allowed to proceed, but with appropriate protections for the rights of study subjects. There was a great deal of discussion about the nature and extent of those protections, and many useful ideas were offered. Since the forum, the FDA, NIH, and PHS have worked closely together to formulate a solution to the challenge of emergency research. This work culminated in the September 1995 publication of a proposed rule⁴⁵ amending the FDA's informed consent regulations. The proposal provided for a

³⁶ *Id.* § 50.23(a)(2).

³⁷ *Id.* § 50.23(a)(3).

³⁸ *See id.* § 50.3(m).

³⁹ *Id.* § 50.23(a)(4).

⁴⁰ *Id.* § 50.23(a).

⁴¹ *Id.* § 50.23(b).

⁴² 42 C.F.R. § 46.116(d)(1).

⁴³ 46 Fed. Reg. 8392 (1981).

⁴⁴ Food and Drug Admin. & National Insts. of Health, Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances, Bethesda, Md., (Jan. 9-10, 1995).

⁴⁵ *See* 60 Fed. Reg. 49,086 (Sept. 21, 1995).

forty-five-day comment period, and the FDA currently is analyzing comments and developing responses.

2. Use of Placebo Controls

Another legal/regulatory/ethical challenge is the use of placebo controls in research. The ethics of placebo-controlled research is an issue that is periodically reviewed in the medical and biomedical literature — and regularly confronted by IRBs in their deliberations. Although the FDA generally does not regard the use of placebo controls as unethical, a series of articles that recently appeared in *The Lancet* and one article in the *New England Journal of Medicine*⁴⁶ dispute this policy and have again put this issue at the fore.

The authors of the articles questioned the continued use of placebo controls in studies of diseases and conditions for which relatively effective medicines are available, such as hypertension, chemotherapy-induced emesis, depression, and congestive heart failure. They argued that detailed informed consent does not vitiate the ethical defects of such studies. Finally, the authors asserted that the FDA's preference for placebo-controlled trials often is not scientifically justified.

The FDA's position regarding the importance of placebo-controlled trials is elucidated in an FDA clinical investigator information sheet entitled *Placebo-Controlled and Active Controlled Drug Study Designs*.⁴⁷ The information sheet deals directly with the placebo-control issues raised.

The difficulties of assessing therapeutic efficacy when active, rather than placebo, controls are used should not be understated. Active control trials can be very difficult to interpret in studies where drug effects can be expected to be small and placebo effects relatively large. While the FDA always has agreed that it is ethically unacceptable to employ a placebo when a study involves serious, irreversible, or life-threatening diseases or conditions for which there is an effective treatment, a distinction can and should be made for less serious or self-limiting conditions — provided that IRBs carefully review and approve the protocol and informed consent procedures. The key issue is the need for subjects to be fully informed through the consent process.

The ethical principle on which the authors of the article in the *New England Journal* based their objection to placebo controlled trials is contained in the Declaration of Helsinki, an international ethical guideline developed by the World Medical Association in 1964 and revised on a regular basis.⁴⁸ This principle provides that all participants (including those in the control group) in therapeutic clinical trials must receive the "best proven" therapeutic and diagnostic methods. If this principle is strictly adhered to, however, it appears impossible to conduct any clinical research once one therapy has been proven effective. Moreover, if all patients must receive the best proven method, it is unclear how substituting an active control for a placebo control resolves the problem, because the experimental treatment being tested is, by definition, unproved.

⁴⁶ Kevin Rothman, *Continued Unethical Use of Placebo Controls*, 331 *NEW ENG. J. MED.* 394 (1995).

⁴⁷ The entire series of Information Sheets for IRBs and clinical investigators was revised in October 1995. This topic is dealt with in revised form in *Drug Study Designs*. The Information Sheets are available from the FDA, Off. of Health Affrs., Rm. 15-22, 5600 Fishers Lane, Rockville, MD 20857; phone (301) 443-1382.

⁴⁸ The Helsinki Declaration was adopted by the 18th World Medical Association in Helsinki, Finland in 1964, and was last amended by the 41st World Medical Association in Hong Kong in 1989. See 21 C.F.R. § 312.120; Council Directive 93/42/EEC, art. I(2)(a), 1993 O.J. (L 169), annex X(2.2). See also, Linda R. Horton, *Medical Device Regulation in the European Union*, 50 *FOOD AND DRUG L.J.* 461 (1995).

3. *Current Relevance of Basic Ethical Documents*

The ethical guidelines that have served for many years as the foundation of human subject protection regulations may need to be revised in light of the new issues raised by contemporary clinical research.

This article has mentioned the difficulties raised in placebo-controlled studies by the “best proven” therapy requirement in the Declaration of Helsinki. This requirement raises other questions. In recent years — particularly since the onset of the AIDS epidemic — there has been a significant shift in views regarding participation in clinical trials. While such participation formerly was regarded as a burden voluntarily assumed by subjects, participation often is viewed now by subjects as a right that will facilitate access to the latest and best, albeit unproved, medical therapy. The line between treatment and research is becoming more difficult to draw, and research subjects often are in the worst position to differentiate between the two.

The role of IRBs in clarifying these issues for subjects has grown in complexity and importance. It also may be appropriate and timely, however, to reexamine some of the basic ethical guidelines in light of current thinking about clinical research design, the perceived benefits of participation in medical research, and the issues raised by new technologies.

B. *Comprehension Challenges*

“Comprehension challenges” is shorthand for the challenges to the FDA to articulate policies and guidelines in a clear manner and to the user community (IRBs, sponsors, and investigators) to seek out and understand needed information. Comprehension issues include: distinguishing between significant and nonsignificant risk medical devices; the differing requirements laid out in FDA and DHHS regulations; women in clinical trials, and the interface between IRB and investigational new drug (IND) regulations; the flexibility of the IRB process under FDA regulations; and the revision of the FDA’s IRB and clinical investigator information sheets.

1. *Significant Risk versus Nonsignificant Risk*

The first comprehension challenge is the need to better educate IRBs about their important role in evaluating studies of medical devices. Specifically, that role involves determining whether or not a device study is “significant risk,” which in turn controls whether or not the sponsor must obtain an investigational device exemption (IDE) prior to proceeding with the study.

Many IRBs are either unaware or do not fully comprehend the requirements of this IDE regulation.⁴⁹ The FDA has attempted to address this problem through the *IRB Information Sheets* and by participating in conferences sponsored by the Office for Protection from Research Risks (OPRR) throughout the United States. The FDA currently is considering additional means that may be helpful to IRBs in this area.

2. *Differing Requirements of FDA and DHHS Regulations*

The FDA also must do a better job in assisting IRBs to identify differences be-

⁴⁹ See 21 C.F.R. pt. 812 (setting forth requirements for IDEs).

tween the regulatory requirements of the FDA and those of the DHHS. The FDA's regulatory jurisdiction derives from the product that is under study; DHHS's jurisdiction, in contrast, derives from the funding source for the study. In some instances both sets of regulations will be applicable. To a large extent, the 1991 issuance of a "common rule"⁵⁰ — after an effort led by OPRR — alleviated the difficulties of complying with conflicting sets of regulations. There remain some differences between FDA and DHHS regulations, however, (such as the FDA's emergency use exception to informed consent) and these must be communicated to IRBs.

3. *IRB and IND Regulations: Women in Clinical Trials*

In 1993, the FDA's Center for Drug Evaluation and Research revised its 1977 *Guideline on the Conduct of Clinical Trials*,⁵¹ a guideline that had discouraged the participation of women of childbearing potential in most phase I drug studies. Phase I studies are those that first expose humans to INDs to assess the drug's acute toxic effects and pharmacokinetic properties. While the purpose of the 1977 *Guideline* to avoid possible harm to a fetus was laudable, application of this rigid guideline had effectively precluded most women from nontherapeutic phase I studies.

The revision of the 1977 *Guideline* was accompanied by a new document entitled *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*.⁵² The new guideline addressed two major points. First, it removed the perceived restriction on the participation by most women of childbearing potential in phase I and early phase II trials. The new guideline encourages the participation of women in early drug trials, provided that pregnancy monitoring as well as precautions against pregnancy are implemented effectively.

The second major effect of the 1993 *Guideline* was to provide notice to sponsors that they must collect gender-related data during drug research and development, and analyze that data for gender effects. A characterization of drug effects by gender now must be part of all new drug applications, and the agency may refuse to file an application that does not include these data. This guideline sets out the FDA's expectation that there will be a fair representation of both genders in clinical trials, so that clinically significant gender-related differences in drug responses can be detected.

What are the implications of this for IRBs? The FDA urges IRBs to scrutinize carefully study protocols that needlessly exclude women or other groups in the drug's target population, or that utilize entry criteria that are needlessly difficult for women to meet. The fact that the FDA wants sponsors to develop certain data, however, is not in itself an adequate basis for an IRB to approve a protocol that it would otherwise reject. Similarly, while a sponsor's decision to exclude women from phase I studies out of concern for potential liability might be reasonable from a purely business point of view, that alone ought not be dispositive for the IRB. IRBs have the discretion to adopt approval criteria that are stricter than those included in part 56 of the regulations.⁵³ Absent a sound medical or safety reason for excluding women of childbearing potential from a

⁵⁰ Office of Sci. and Tech. Policy, Federal Policy for the Protection of Human Subjects; Notices and Rules, 56 Fed. Reg. 28,003 (1991).

⁵¹ CENTER FOR DRUG EVALUATION AND RESEARCH, FDA, GUIDELINE ON THE CONDUCT OF CLINICAL TRIALS, DHHS Pub. No. (FDA) 77-340 (1977).

⁵² CENTER FOR DRUG EVALUATION AND RESEARCH, FDA, GUIDELINE FOR THE STUDY AND EVALUATION OF GENDER DIFFERENCES IN THE CLINICAL EVALUATION OF DRUGS, Dkt. No. 93D-0236 (1993).

⁵³ See *supra* text accompanying note 27.

study, however, an IRB should consider such exclusion in light of the express requirement that subject selection be "equitable."⁵⁴

4. *Flexibility of IRB Process*

To cope with an enormous workload (approximately two hundred protocols per month), one IRB had implemented a system of apportioning protocols to panels of IRB members. Based on the recommendations of the panel, the entire IRB would vote on the protocols. While this IRB possessed impressive levels of medical expertise and a genuine commitment to doing a thorough job, the FDA determined that these procedures did not comply with the requirements of the IRB regulations.

The IRB regulations require that *all* IRB members have an opportunity to review the protocols on which they vote. If innovative measures can be taken to streamline the IRB review process without compromising the quality of IRB review or violating the regulations, the FDA will consider those measures.

5. *Revision of IRB and Clinical Investigator Information Sheets*

The FDA is in the midst of reviewing and revising its primary guidance documents in the area of human subject protection: the IRB Information Sheets and the Clinical Investigator Information Sheets. Based on comments received since their initial publication, these sheets are helpful to many IRBs. It has been some time, however, since the Information Sheets have undergone a major, substantive revision, and this is a propitious time to incorporate some of the agency's new policies and regulations into the Information Sheets.⁵⁵

IV. CONCLUSION

In the past, the FDA has addressed successfully the human subject protection challenges that have come before it. One example was the agency's promulgation in the month prior to the Persian Gulf War of the informed consent exception for certain combat situations.⁵⁶ Formulating effective and feasible solutions to the challenges addressed in this article will require creativity and cooperation among sponsors, the IRB community, and the FDA.

⁵⁴See 21 C.F.R. § 56.111(a)(3).

⁵⁵See *supra* note 47.

⁵⁶See 55 Fed. Reg. 52,817 (Dec. 21, 1990).