

Chapter 2

Ethics and the IRB

You're on the Institutional Review Board. Congratulations!

2.1 Your Influential Position

IRB permission is required for most research with people, including research regulated by the FDA or funded by the NIH. Typically, the scientist or scholar submits a proposal; the IRB approves it, rejects it, or returns it with instructions for changes. Most IRBs are situated in hospitals, government agencies, and institutions of learning (including universities, medical schools, and research institutes); the rest are independent, either nonprofit or for profit. All follow the same rules.

This manual shows how to apply ethics in the daily operations of your IRB. It addresses the issues and dilemmas you will face as an IRB member and articulates the competing considerations you will need to balance. I host a website about ethics review at <http://balancedethicsreview.com> and invite you to join the conversation there.

If you are new to the IRB, you should give careful thought to the conditions of your service (see Sect. 2.6). If you are a community member, please see especially Sect. 2.6.3.

Your seat on the IRB puts you in a pivotal position in deciding what research will be permitted. You will review the ethics of research from academic niches in every corner of your university or medical school. Some new IRB members worry that they will be

unequal to this responsibility, but not be intimidated. You don't need a doctorate in theoretical ethics. You need only learn the basics of practical ethics and regulation, and apply the relevant evidence.

2.2 Evidence

If ethics seems like an abstract field, you will be relieved to learn that your committee's deliberations are supported by a substantial body of evidence. Should you protect subjects from a survey about an upsetting experience? You don't have to guess—others have done the research to answer that question (see Sect. 6.5). How much do people sacrifice when they enroll in a typical randomized trial? The question has been carefully studied (see Sect. 7.3); there's no need to speculate when we have data.

I will point out when the data are meager, and often encourage your IRB to fill the evidentiary lacuna. This research would sometimes require little more than a willingness to examine the records your committee generates in its routine operations (see Sect. 9.1).

2.3 Scandal

We begin our discussion of ethics review with two notorious experiments at the heart of the IRB system's history.

In the 1950s, Chester Southam, a scientist at Sloan-Kettering in New York, began a series of experiments to understand our bodies' response to malignancies—how we fight off cancer or succumb to it. This promising research led Southam into moral failure when, in 1963, he injected live cancer cells into patients in the Jewish Chronic Disease Hospital in Brooklyn without their consent. His subjects suffered no significant physical harm but his violation of their dignity was shocking (Katz et al. 1972, p. 9–65).

The most infamous experiment of twentieth-century America was the Tuskegee syphilis study, which lasted from 1932 to 1972. During those 40 years, government doctors actively kept poor black sharecroppers with syphilis from obtaining treatment. The infection invaded their hearts and brains; some died. The scientists took careful notes.

2.4 Research Ethics

Even morally sound medical progress comes at a price. Polio vaccines could be developed only through trials that cost some children their lives. This research was not immoral, for the scientists used the safest methods available. In contrast, the effectiveness of new antibiotics was sometimes proven by withholding them from patients in need (Beecher 1966).

Research ethics, which examines the moral dimensions of research, blossomed in this time of promise and peril. Hans Jonas, a philosopher, Paul Ramsey, a theologian, and Henry K. Beecher, a doctor, were among the first in the field (Beecher 1966; Jonas 1969; Ramsey 1970). Beecher, the Henry Isaiah Dorr Professor of Anaesthesia Research at Harvard, exposed dozens of unethical investigations in his classic article (Beecher 1966); we will refer to it regularly.

We will also draw on the Belmont Report (National Commission 1978). One of the most respected documents in research ethics, the Report instructs your IRB to honor the moral principles of beneficence (concern for the welfare of others), respect for persons (concern for the rights of others), and justice.

Many aspects of research are ethically salient. Your IRB acts morally when it protects research subjects; scientists act morally when they discover new treatments for disease.

2.4.1 *Two Ethical Principles*

This manual rests on two ethical principles. As responsible people, we have (at least) two obligations:

- Do no harm to others, and
- Help others.

These obligations, which bind individuals and groups alike, are part of our social covenant. Your responsibility as a member of the IRB is shared by the other members, and your committee as a whole should act ethically. Similarly, your moral obligations extend to both individuals and groups.

2.4.2 *Two Ethical Goals*

The two principles translate directly into your IRB's two ethical goals: to protect subjects and to enable research that will benefit society.

Research ethics has traditionally focused on protecting human subjects from injury ("do no harm"), but that is only one piece of the picture. The other ethical centerpiece is the role of scholarly and scientific investigation in improving our health and our society ("help others"). It is, for instance, highly ethical to conduct research that reduces the burden of cancer, lessens the disparities in health between rich and poor, or exposes racial discrimination.

2.4.3 *Goals into Practice*

Much of the unethical research of the 1950s and 1960s was federally supported and a serious embarrassment for the funding agencies. James Shannon, director of the NIH, and his colleagues were determined to take action, but they faced a practical problem: what rules—what system—would block abusive studies without hindering ethically sound research? For an answer, they turned to a model close at hand.

NIH has its own hospital, the Clinical Center. In 1953, Center leaders formed the Clinical Research Committee to review potentially hazardous research (Frankel 1972, p. 10–12; Stark 2012, p. 75–77). This proto-IRB reduced but did not eliminate subject risk, allowing research that presented some risk so long as subjects were informed and gave their consent (Stark 2012).

The twin goals of the IRB system—safeguarding subject safety and enabling research intended to benefit the public—are a matter of historical record. In 1965, Shannon discussed the governance of science with a Public Health Service (PHS) advisory board. The PHS, Shannon said, planned to keep experiments on a sound ethical basis by means of "terms and conditions" that included the IRB system, which was only months from its launch. The PHS, he continued, had "a dual responsibility. One is a minor one of keeping the Government out of trouble ... but really the major one is through these programs to try to encourage the development of terms and conditions that will encourage the flourishing of sound clinical investigation rather than discouraging it" (quoted in Frankel 1972, p. 31).

My belief that balanced review is essential rests not only on the historical record, but on societal expectations. The public, which was appalled at the research scandals of the postwar period, also relies on scientists to lessen the common burdens of our humanity.

In 1966, the PHS, under Shannon's leadership, directed institutions receiving agency funds to establish committees along the NIH model, thus creating the IRB system. Early IRBs were keenly interested in permitting research to proceed once they were confident that subject safety had been adequately safeguarded; they thus conducted balanced review.

2.4.4 *Today's Loss of Balance*

This balance has largely been lost (Brendel and Miller 2008); some authors even encourage IRBs to believe that their only concern should be subject safety. One manual asserts, "The regulatory mandate is clear: human subject protection, first, foremost, and last" (Shamoo and Khin-Maung-Gyi 2002, p. 58).

This statement would have been seen as bizarre at the system's birth; in 1966, nobody talked about subject protection as the IRB's sole concern. But by 1977, an observer remarked, "Peculiar to this time is the need to restate a proposition that, a decade ago, would have been regarded as self-evident, namely, that fostering excellence in medical research is in the public interest" (Eisenberg 1977).

Other ethicists have noted the contemporary tendency to focus exclusively on subjects. In 2007, a federal agency ruled that an experiment that found a new way to reduce hospital infections had violated the rights of its subjects. Ruth Faden, director of the Institute of Bioethics at Johns Hopkins, objected to this one-sided oversight: few people, she said, "have come forward to express concerns and oversight for the thirty thousand or so people who will die unnecessarily each year in the United States from this type of infection" (Faden et al. 2013). Her recognition of the value of research echoes the words of Hans Jonas, a philosopher who in 1969 praised science's struggle to combat disease and promote health and life. This "expansive goal," he said, has "the nobility of the free, forward thrust" (Jonas 1969, p. 230). Subjects themselves believe, sometimes passionately, that biomedical research saves lives, and they may be eager to participate even when it involves risk.

None of this is to say that social welfare should override individual rights. Jonas himself exhorted us never to permit subjects to be abused for the good of society (Jonas 1969). But when the question is not of abuse, but of risks that some subjects would willingly accept, the overprotection of subjects is an error. Educator and ethicist Rosamond Rhodes asks us not to try to protect subjects “from *any* risks, regardless of how unlikely, fleeting, or trivial the anticipated harm. When the physical and other risks involved are negligible and unlikely, and the study promises to provide a societal benefit, a reasonable assessment should conclude that the balance tips toward promoting scientific advance” (Rhodes 2014, emphasis in original).

2.4.5 *It’s Always About People*

The balance your IRB should seek can be expressed in two ways: as “subject welfare versus scientific advances” or as “subject welfare versus societal benefit.” Rhodes includes both formulations because they are not identical. For your IRB, science matters, not in its own right, but because it helps people. Scientific advances are a means to the end of societal benefit.

Successful biomedical scientists enjoy funding, promotion, and prestige, but these are only proxies for the value they create. Their work attains moral power because their discoveries save lives and reduce suffering. Similarly, research in the social sciences matters because society benefits when scholars expose plagues like racial discrimination. When I discuss the IRB’s duty to “permit research to be conducted,” that is a contraction for “permit research that will increase the well-being of society.”

The word “society” is itself a contraction. Your IRB’s duty is to the individuals who form society—to all of us as we struggle with illness, care for others, and confront injustice. Political philosopher Alan Wertheimer astutely observes, “It is often said that medical research exhibits a tension between science or progress or a ‘greater social good’ and the interests or rights of the individual. Although that way of putting things is not wrong, it is also misleading. After all, ‘society,’ and ‘science,’ and ‘progress’ do not describe metaphysical entities that are not reducible to the interests of individuals. Rather, they

are different ways of describing the interests of discrete, albeit statistical, individuals.” This does not resolve the ethical choices your IRB must make. “There may sometimes be a tension between the interests of individuals who serve as research subjects and the interests of individuals who stand to gain from such research. But it’s individuals versus individuals all the way down” (Wertheimer 2011, p. 5).

Your IRB will have constant contact with scientists and scholars. They deserve every opportunity to achieve their professional goals. But their primary claim on your ethical judgment is derivative of the need of the people, unknown and perhaps unborn, who will benefit.

Dennis Mazur, who is a professor of medicine, senior scholar in ethics, and long-time IRB chair, cautions your IRB against becoming “a force for the promotion of research” (Mazur 2007, p. 222). Mazur is right on two counts. While research is important, subject protection must never be forgotten. Further, your IRB never actively promotes research; you merely make it possible for others to conduct it, by protecting subjects from harm, facilitating informed subject choice, and providing scientists with an objective third party to guard them from error.

2.5 Ethical Goals and Regulatory Means

Your IRB’s decisions should be respected because they are ethically persuasive; they must be obeyed because you hold federal power. You pursue ethical goals through regulatory means.

2.5.1 Principles of Regulation

Regulation, like ethics, has its own principles. Responsible regulators honor these virtues:

- Respectfulness
- Transparency, by operating on the basis of rules that are known to all
- Efficiency, by seeking maximal benefit at least cost to all parties
- Clarity, by using language in ways that make communication easy

- Accountability, by justifying their decisions and reconsidering them when questioned
- Judiciousness, able to distinguish significant from trivial
- Rationality, striving to improve the public interest in ways that are based on evidence
- Restraint, acting only within the scope of their authority

These principles are discussed in Sect. 3.1. Your IRB should follow both ethical and regulatory best practices.

2.5.2 Organization and Legal Framework

Your IRB is part of a multitiered system of oversight (Halpern 2008). You look over the scientist's shoulder, and government officials look over yours.

During the 1970s and 1980s, federal funding agencies realized that they had no method in place to protect subjects. Multiple agencies implemented rules for ethics review, no two alike; IRBs struggled to keep track of which agency required what. This regulatory jumble was unsnarled in 1991, when the Department of Health and Human Services (HHS) and 14 other federal departments and agencies agreed that all would follow a single set of regulations; this is known as the Common Rule (45 CFR 46 Subpart A). The FDA simultaneously modified its regulations to be nearly identical to the Common Rule (21 CFR 50 and 56).

The OHRP, which is within the NIH, and the FDA have primary responsibility for oversight of IRB operations. Your committee's relationship with these two agencies is central to your effective functioning (see Chap. 8 for more on this topic). Your IRB may also be guided by state or local regulations, which are outside the scope of this manual.

2.6 Your IRB Service

You should be proud of your work on the IRB, but pride should not be your only reward. You should serve on equitable terms, fairly compensated and adequately protected.

2.6.1 Compensation

In some institutions, IRB service is undemanding, but many IRBs have long meetings (2 or 3 h is not uncommon) with substantial additional time spent in preparation. Joining the IRB is a significant commitment.

If you are not yet a member, you need to decide if the terms you are offered make sense. If you are a junior faculty member, your department may require committee service as a condition for tenure, but excessive time spent outside your core responsibilities will jeopardize your future. Many IRBs require far more work than any other institutional committee.

Some institutions pay IRB members for their service, either in cash or by releasing them from other obligations. Others do not, on the ground that everyone has an obligation to participate in the institution's governance; this approach may be revisited if new members prove hard to recruit.

If your department chair indicates that he or she will be grateful if you agree to serve, ask if that gratitude will be manifested in some concrete fashion. Pediatrician and ethicist Daniel Nelson advises that the institution "should send a clear signal that IRB membership is a necessary and important activity and recognize such service when considering promotions, tenure, and clinical work schedules" (Nelson 2011, p. 108). One particularly welcome signal is for the institution to pay your department for time spent on IRB duties, so that the department can compensate you.

If you are invited to serve on the IRB and are unsure what to do, contact current committee members and ask what their service is like. Be a good citizen but not a martyr.

If you are the non-affiliated, non-scientist, or community member, some institutions won't pay you, some will, and some will only if you ask. Some community members enjoy their service and don't mind being unpaid; others will not work without compensation. It's your choice.

2.6.2 Protection from Lawsuits

It is unusual for IRB members to be sued for their work on the committee, but it does happen (Halikas v. Minnesota 1996; Icenogle 2003; Berrett 2011; Looney v. Moore 2013). Your institution should

promise to furnish you with legal defense and pay any financial penalty assessed against you (Nelson 2011). I will wager that the members of the Board of Trustees have this protection as they undertake their official duties. Have they extended it to you?

2.6.3 *The Community Member*

Every IRB must have at least one member who is not affiliated with the institution and at least one member who is not a scientist (21 CFR 56.108(c-d), 45 CFR 46.107(c-d)). Many IRBs use a single person, an unaffiliated nonscientist, to fulfill both roles. A member who serves in either or both roles is often called the community member, although the regulations do not use that term.

Commentators do not agree on what the role of the community member should be (Klitzman 2012a). In 1969, when the IRB system was rapidly evolving, legal scholar Guido Calabresi speculated that the doctors on review boards would be reluctant to expose subjects to significant risks. The nonscientists, Calabresi guessed, “would tend, on the whole, to approve some experiments that would not now be passed. This is especially true where the potential gains from an experiment are great, but the risks involved are also great.” He predicted that lay people would be less inclined than doctors to fear lawsuits or to feel there was a special obligation to the subject, and “more likely to give greater weight to society’s long-run interest” (Calabresi 1969, p. 400). Thirty years later, the National Bioethics Advisory Commission took the opposite position, seeing the community member as representing potential research participants, not society at large (National Bioethics Advisory Commission 2001, p. xvi).

In the absence of consensus, you as a community member can serve in any way that makes sense to you and your IRB chair. Your contributions, like those of every other member, will be dictated by your abilities. If you are a high school art teacher and every other member of the committee is a medical specialist, you are unlikely to understand the protocols in the same depth as they. You don’t have to, and that is not why you are here. You bring an outsider’s perspective that the board needs.

Robert Levine, the Yale scholar who is one of the IRB system's intellectual architects, expresses the proper role of the community member beautifully. "The layperson-members should be assured that each and every IRB member is a part of the laity with regard to the specialties of some or all others. They should work together in a climate of trust that each will contribute according to his or her abilities to the overall function of the IRB" (Levine 2006b, p. 61–62).

2.7 The Triumph of Ethics Review

From the start, the IRB system dramatically reduced unethical experiments, including those that enlisted subjects without their consent (Curran 1969). Jerry Menikoff, before he became head of OHRP, wrote, "By any standard, it must be recognized there has been a massive change with regard to informed consent, and all for the better." The problems of unethical research in the 1960s, "people being enrolled in studies without their even knowing they were in a study ... seem to be from a very different world" (Menikoff and Richards 2006, p. 85).

The best-documented example of a successful early IRB was at Case Western, where the dean of the medical school led the committee and the members were all department chairs. This committee conducted careful review without unduly encumbering research (Cowan 1974). Research subjects no longer had to trust the integrity of the investigator, because someone else was looking after the subject's welfare. This is the triumph of ethics review. It is an important contribution to society, and I hope it is one of the reasons you are willing to serve on the IRB.

Balanced Ethics Review

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