

Minimizing Risk in Clinical Research

The randomized clinical trial, the gold standard of modern clinical investigation, is a remarkable social construction. Its overall goal is the scientific demonstration that a new drug or device produces a health benefit that justifies its risk. Ultimately, the therapeutic fruits of all biomedical advance have to be submitted to this scrutiny before they can enter clinical use.

Normal volunteers and patients are by far the most important participants in the process. Since many of these are in the group receiving the placebo, and since many trials fail, many sick and well participants have little likelihood of benefiting in the trial. The protection of these individuals from harm is therefore a compelling moral responsibility.

Three pillars undergird this morality. One is the evolution of ethical statements about human research that began with the Nuremberg trials and have undergone several major reconstructions since that time (1). The most familiar of these is the Belmont Report (2), which emphasized the autonomy of the participants (in deciding whether to consent); the respect for persons (in the investigator's design of the trial); and beneficence (in minimizing the risk facing volunteers). The second pillar of protection is the institutional review board (IRB), a group of necessarily fallible humans charged with reviewing a research proposal for its importance, scientific merit, feasibility, and risks and benefits to participants. The final pillar is informed consent, the process in which a potential participant is told about the study and its risks and decides whether or not to commit. Regrettably, all three bulwarks have weaknesses.

The complexity of modern science and the power of its potential interventions provide new challenges to the very broad guidelines of the Belmont and other reports (1, 2). Just think of gene transfer and stem-cell research if you doubt this. Institutional review boards are beleaguered by the number of protocols, the complexity of the studies, the range of required expertise, the potential conflicts of interest of both investigators and institutions, and the nuances of the risk-benefit calculus (3). And truly informed consent is extremely difficult to structure, provide, and measure (4).

It would be helpful if proposed solutions to perceived risks could be tailored to the fractional likelihood of harm from participating in research. How many people are currently involved in clinical trials? Published figures for the United States range from 2 000 000 to 20 000 000. How many experience significant harm? That number too is unknown. But some high-profile cases, stridently reported in the press, have created an impression that there are serious problems crying out for remedy. Proposed correctives include exhortation, regulation, and litigation. All are being actively pursued. A recent report from the Institute of Medicine emphasized voluntary efforts to establish a new

level of safety and ethical conduct (5). The Institute of Medicine committee recommended that all human research take place within human research participant protection programs, that the leadership of these programs be publicly and materially committed to the highest ethical standards, that all "who make decisions" within the research protocols have training in the ethics of human studies, that participants be given enhanced roles in the design and conduct of protocols, that scientific and conflict of interest review be scrupulously completed before a final ethics consideration, and that the IRB be renamed and reconstituted as an ethics review board. In addition, the Institute of Medicine committee urged that a new approach to informed consent be developed.

Regulation and legislation are also being given greater weight. The Office of Human Research Protection and the Food and Drug Administration have raised the standards for human protection and introduced closer monitoring and program accreditation as a means of achieving excellence. Senators Kennedy and Frist have initiated legislation that would require the level of excellence and care urged in the Institute of Medicine report.

The paper by Mello and colleagues in this issue (6) describes the growing importance of the third approach, litigation. Injury sustained in research has attracted public interest, and recent suits have expanded the adversarial challenge in three ways. There is a greater diversity of claims, including allegation of investigator and institutional fraud or deception, which carry higher penalties and award potential. There is a wider array of targets, now including IRBs and their members. The negative effect on voluntary participation is obvious. And there are many more plaintiffs as the use of class action suits gains momentum. This development can only add to the already impressive costs of IRB efforts, as quantified for multicenter studies by a letter in this issue (7).

Where do these conflicting influences leave us? Scientific progress is not going to slow down. The generation of ideas and products that could benefit healthy and sick people throughout the world is not going to go away. And testing in human beings will be indispensable for the indefinite future. Such testing cannot be rendered absolutely risk free. But it should be organized in systems where the highest ethical standards, annealed to adequately resourced procedures, minimize risk. When harm occurs, the Institute of Medicine report urges that the system compensate for injury and expense. Except for egregious lapses, the system and not the individual should bear the blame and the cost (8). All this should be manageable without either excessive expense or loss of individual autonomy and value.

It may be unrealistic to try to insulate clinical research from litigation directed at the truly unfortunate lapses we

have witnessed in the past several years. But before litigation gets a stranglehold on clinical research, I would urge that we interpose a panel of disinterested review between injury and suit. I would make the outcome of this analysis available to both litigants and judges so as to minimize captious claims and inform appropriate ones. Even more, however, if reconciling the pursuit of new knowledge with an inevitable minimum of risk and an individual's freedom to sue proves impossible, society should construct a compensating procedure in which scientists, research participants, and lawyers cooperate to allow progress. This would serve the image of research as a public good, benefiting all, before litigation around research harms degenerates to the malpractice crisis that today complicates the efforts of practicing physicians to do no harm in the struggle against disease and toward health.

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Potential Conflicts of Interest: None disclosed.

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Ann Intern Med. 2003;139:71-72.

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