

Remaining Faithful to the Promises Given: Maintaining Standards in Changing Times

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In the last three years, the clinical research establishment has moved from a sleepy backwater to center stage. It has invaded the headlines of the media,¹ focused the attention of various courts,² and appeared in scholarly literature with dire warnings of irremediable negative effects of investigator conflicts of interest.³ This is not surprising given how rapidly the stakes have escalated in recent times. Huge profits surround the prospect of clinical success in discovering new drugs or devices that satisfy the American public's desire for increased longevity and enhanced quality of life.⁴

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¹ See, e.g., Kurt Eichenwald & Gina Kolata, *Drug Trials Hide Conflicts for Doctors*, N.Y. TIMES, May 16, 1999, at A1; Kurt Eichenwald, *U.S. Officials Are Examining Clinical Trials*, N.Y. TIMES, July 14, 1999, at C1; Kurt Eichenwald & Gina Kolata, *A Doctor's Drug Trials Turn Into Fraud*, N.Y. TIMES, May 17, 1999, at A1; Kurt Eichenwald & Gina Kolata, *Hidden Interest—A Special Report; When Physicians Double as Entrepreneurs*, N.Y. TIMES, Nov. 30, 1999, at A1; Sheryl Gay Stolberg, *Study Says Clinical Guides Often Hide Ties of Doctors*, N.Y. TIMES, Feb. 26, 2002, at A17; Marc Kaufman, *Clinical Trial Sanctions Urged; HHS Plans to Tighten Controls to Protect Patients in Tests*, WASH. POST, May 24, 2000, at A2; Robert O'Harrow, Jr., *Companies' Influence on Medical Studies is Feared*, WASH. POST, Aug. 16, 2000, at A8; Rick Weiss & Deborah Nelson, *Gene Therapy's Troubling Crossroads; A Death Raises Questions of Ethics, Profits, Science*, WASH. POST, Dec. 31, 1999, at A3.

² See, e.g., *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807 (Md. 2001); Deborah Nelson & Rick Weiss, *Penn Researchers Sued in Gene Therapy Death—Teen's Parents Also Name Ethicist as Defendant*, WASH. POST, Sept. 19, 2000, at A3; Rick Weiss & Deborah Nelson, *Penn Settles Gene Therapy Suit; University Pays Undisclosed Sum to Family of Teen Who Died*, WASH. POST, Nov. 4, 2000, at A4.

³ See, e.g., Bernard Lo et al., *Conflict-of-Interest Policies for Investigators in Clinical Trials*, 343 NEW ENG. J. MED. 1616 (2000); S. Van McCrary et al., *A National Survey of Policies on Disclosure of Conflicts of Interest in Biomedical Research*, 343 NEW ENG. J. MED. 1621 (2000).

⁴ See Julie Appleby, *Bayer Triples Anthrax Antibiotic Production*, USA TODAY, Oct. 17, 2001, at 1B; see also David Eggert, *Lilly's New Bone Drug Lauded; Forteo Offers New*

Notwithstanding the potential profit, clinical research is always ethically problematic because it pits the best judgment of the care provider against a predetermined research plan. As Hans Jonas commented many years ago:

Progress is an optional goal, not an unconditional commitment, and . . . its tempo in particular, compulsive as it may become, has nothing sacred about it. Let us also remember that a slower progress in the conquest of disease would not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having.⁵

Two decades later, the analysis remains the same.

In these remarks, I will briefly address the following five areas of concern: (1) review and monitoring of research in diverse settings; (2) ensuring the adequacy of the informed consent process; (3) determining who, among those who profit, should assume the costs of adequate protection for human subjects; (4) redressing the vast variation in standards that govern research with those who cannot clearly provide legally and ethically adequate consent; and (5) enhancing the ethical sensibility of the research community.

I. REVIEW AND MONITORING OF RESEARCH IN DIVERSE SETTINGS

The extension of research protocols into the previously untapped resource of the physician's office is one of the prime features of the intellectual and logistical topography of the modern research enterprise. This development satisfies a number of goals for those planning and conducting large clinical trials. First, it provides a setting for pharmaceutical companies, which assures a supply of patients suited to particular protocols. Second, patients like to go to the small, private offices of their physicians because they are personal and non-intimidating. Third, in a well-run office, appointments are

Treatment for Osteoporosis; Could Bring in \$500 Million Yearly, Experts Say, INDIANAPOLIS STAR, June 24, 2000, at 1C; Jeff Gerth & Sheryl Gay Stolberg, *Medicine Merchants: Birth of a Blockbuster; Drug Makers Reap Profits On Tax-Backed Research*, N.Y. TIMES, Apr. 23, 2000, at A1; Luke Timmerman, *Demand, Marketing Bolster Sky-High Price of New Biotech Drugs*, SEATTLE TIMES, Apr. 28, 2002, at A1; Theresa Waldrop & Kristin Jensen, *Miracles in a Bottle; Blockbuster Cures Boost Fortunes*, CHI. SUN-TIMES, Aug. 8, 1999, at 49.

⁵ Hans Jonas, *Philosophical Reflections on Experimenting with Human Subjects*, 98 DAEDALUS 245 (1969), reprinted in JAY KATZ, *EXPERIMENTATION WITH HUMAN BEINGS* 148 (1972).

thoughtfully scheduled and often occur on time. Access is easy, parking is available, and more homogeneous populations may be served.

In contrast, the academic medical center has become the colossus of modern medicine: vast entryways lead to miles of corridors, and befuddling arrays of color-coded signs attempt to direct patients to the right destination. Who would want to participate in research in such an intimidating setting? Even clinical centers designed to attract possible research participants still retain some of these features of an academic medical center.

Conducting research in the private doctor's office generally distances the company from the review of an academic medical center's institutional review board (IRB) and places the review under the aegis of a private IRB. The extensive delays that accompany review by the academic medical center cannot plague private review; private review, however, lacks the in-depth scrutiny that adequate review by independent scholars should provide. I have recently heard presentations by the heads of two independent IRBs. Each has panels that meet frequently and each provides review and approval, in general, within one week.⁶ Each has experts available to review the science of the protocol and assess whether the “[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.”⁷

There are two ways in which to approach this intellectual calculus, often referred to by the shorthand of the “risk/benefit ratio.” It may be parsed from the basis of technically adequate expertise, or it may be approached from broad-based scholarship and, in some cases, from wisdom. Judgments about the importance of knowledge are distinctly difficult to make about new areas of research. Is the pursuit of another “me too” drug for the treatment of the symptoms of chronic illness an acceptable goal that justifies exposing subjects to risk? If adequate drugs already exist, will this one, if successfully tested and marketed, add anything to generalized knowledge? What if this drug will be far cheaper and will increase

⁶ William Jacobs, Testimony to the Committee on Assessing the System for Protecting Human Research Subjects, National Academy of Sciences, Institute of Medicine (Nov. 2001); Carol Saunders, Testimony to the Committee on Assessing the System for Protecting Human Research Subjects, National Academy of Sciences, Institute of Medicine (Aug. 2001).

⁷ Basic HHS Policy for Protection of Human Research Subjects, Criteria for IRB Approval of Research, 45 C.F.R. § 46.111(a)(2) (2002) (emphasis added).

access to therapy? IRBs are directly precluded from considering whether the long-range public policy impact of their decision may be the raising or lowering of costs of medicine.⁸ In addition, the FDA regulations require the company to demonstrate that the drug is safe and effective, not that it is better.⁹ How should an IRB balance all of these factors? I would argue that this must be approached with the wisdom that comes as the result of years of research and thoughtful efforts at design and at patient care—that is, from experience.

Thus, in the “best of all possible worlds,” as *Candid* might sing, the IRB would evaluate the protocol against the most elegant design and suggest changes that might bring results more quickly or produce results more definitively, thus limiting the exposure of subjects to risk. This type of review is less critical for two kinds of proposals: those developed by large drug companies, which have teams of designers assigned to create and refine the design of research; and those submitted to the National Institutes of Health (“NIH”), which undergo peer review by qualified study sections. But in-depth design review is absolutely essential for protocols initiated by academic investigators that have not endured these sorts of review. This is the case with protocols that will *not* be submitted for drug company or NIH funding because they require small amounts of money, or because they are submitted to private foundations with little expert capacity. Whether the commercial IRBs can muster this sort of deep expertise has not yet been demonstrated, though recent events prove that academic IRBs often fall far short of the mark. Ideally, review should be by a cohort of qualified researchers whose comments in a congregate setting encourage deep analysis.

The problem of conflict of interest must also be addressed, as many critics of IRBs have recently pointed out. Not all conflicts involve direct financial benefit: the appeal of promotion and academic stature rank also pose potential problems. A private IRB that takes too long to review a protocol, makes too many changes, and gets the reputation for being obstructive rather than facilitating will not be in business for very long.

Finally, the diffusion of research to locations outside of the academic medical center scatters responsibility so that authority is not challenged. Historically, when most medical research was funded by

⁸ *Id.*

⁹ See Applications for FDA Approval to Market a New Drug, 21 C.F.R. § 314.2 (2002).

the NIH, protocols were conceived of by groups of academics. These academics submitted the design for peer review, reviewed the data as they accumulated, and assessed the aggregate data before formulating the written product and submitting it to another layer of intense scrutiny by peers before publication. When research is diffused, the scrutiny by the company proposing the research is focused on accumulation of data quickly as a support for the FDA approval process—a good thing if the goal is to limit unnecessary risk to participants. All other aspects of the process, however, are also under the exclusive control of the company—including review of the data, analysis of the data, drafting the article, and reaching the conclusions. The company has one goal required by its fiduciary obligations to shareholders: maximizing profit. This goal is not compatible with dispassionate review of the data, reference to other like compounds and studies, and evenhanded conclusions. This process is further complicated by the fact that the names of well-recognized academics are frequently attached to the publication even when they have participated hardly in any stage of the process.¹⁰

II. ENSURING THE ADEQUACY OF THE INFORMED CONSENT PROCESS

As a professional honed in the era of rights movements, I believe that everyone should be animated by passions. One of mine is the total inadequacy, or lack, of a process for informing patients or normal healthy volunteers about the possible risks and benefits of research—that is the inattention to a robust form of individual informed consent. A second and related outrage is directed to the forms that purport to present the outline of research including its design, risks, and benefits. Let me begin with the latter.

The idea of informed consent first appeared in a law case in 1957, although the ideas have been a part of legal and ethical consideration for over a century. The components of informed consent are clear and include notions of self-determination, empowerment, and reference of abstract ideas to the personal idiosyncratic values. But something happened to the doctrine of informed consent on the way to the ball: it got mugged by the corporate, institutional, and administrative risk managers whose focus is singular and is directed at the goal of protecting the entity, whatever its form, from possible later liability, not on empowering the

¹⁰ Thomas Bodenheimer, *Uneasy Alliance—Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539 (2000).

patient to make the most individually appropriate decision. This goal—and no other—is reflected in “informed consent” documents, which neither inform nor empower, but rather dump all of the possibly foreseeable—however remote—risks on the patient. How is a patient to distinguish the most important of these risks, those of serious impact and frequent occurrence, from the less significant? With the exception of possibly teratogenic drugs, which usually come with warnings in bold and capital letters—again for risk management reasons—the rest of the form disappears into the tombstone gray of endless, invariable discourse.

Informed consent forms regularly run from eight to sixteen pages of single-spaced recitation. They are barriers to, rather than supports for, critical individual thinking. What they do is calm the worries of the risk managers whose job it is to get all of the most contingent possible risks onto the paper trail of the research. Things are not as dire in the clinical care context, as fewer professionals are involved in the process, and the discussion is likely to be directed by the responsible clinician who has some relationship with and commitment to the patient. In the context of research, the potential subject and the researcher are likely to be strangers, and the conversation is thus totally in the hands of the planners and designers. When the suggestion was offered that these forms be accompanied by a “road map” to give the subject some idea of relative and most important risks, the liability attorney present at the discussion vetoed the idea. He offered the logic that the road map would substitute for the indigestible reality of the form and would not protect the sponsor and the investigator.¹¹

Creative alternatives are not beyond conception. Disclosure forms might contain layers of information—the most relevant in the body of the form, and the least important in an appendix. Potential research subjects could choose the level of risk of interest to them. The data could be placed in categories of risk described in the document with references for further research. Some patients and subjects have an almost inexhaustible thirst for information, seeking their own answers on the Internet, whereas others are content to accept the statement of the researcher that this is a good protocol to join. The former should be respected, and the latter—who need

¹¹ James Phelps, Remarks at the Meeting of the Committee On Assessing the System for Protecting Human Research Participants of the National Academy of Sciences, Institute of Medicine, Aug. 21-22, 2001.

help evaluating research possibilities—are further deterred from undertaking such an evaluation by the current impenetrable process.

What should a better informed consent process look like? We know how an empowering discussion with a potential subject could be conducted. First of all, it would have to be a process that engages the subject on an escalating plane of complexity and abstraction. It would have to begin with the fact that this is research and that we do not know the answer to the question posed. In some cases, it means that we do not yet appreciate all of the risks and cannot predict what the consequences will be. In others—randomized clinical trials of approved interventions—it means that we do not know which is best. In placebo-controlled trials, it means that we do not know if the intervention proposed is better than no intervention at all. Evaluating the reading levels of the language of the informed consent documents has become the norm. But understanding the language may not provide real facility with the concepts. We can teach about these concepts as a precondition to engaging the potential subject. All it requires is time and money.

III. DETERMINING WHO, AMONG THOSE WHO PROFIT, SHOULD ASSUME THE COSTS OF ADEQUATE PROTECTION FOR HUMAN SUBJECTS

Unfortunately, no one really wants to pay for an adequate process. The NIH does not approve, as part of the direct costs of a protocol, the costs of protecting human subjects. The Human Genome Project allocated only three to five percent of the total costs of the endeavor for an exploration of the legal, ethical, and social aspects of the research.¹² It would not be unreasonable for the NIH or the pharmaceutical companies to provide support for a genuinely informing and empowering process. This elaborated, reality-based approach would not only respect the needs and rights of the potential subject, but could conceivably enhance adherence to the protocol. In any event, it would be preferable to the charade that now masquerades as “informed consent.”

Adding to the cost of research is not an attractive idea for either the NIH or for industry. No one wants to pay for airport security either, and we have evidence of the results of this short-sighted policy. For the academic medical center, where a large (though now

¹² See U.S. Department Energy Office of Science, *About the Human Genome Project*, at http://www.ornl.gov/TechResources/Human_Genome/about.html (last visited Apr. 30, 2003).

diminishing) percentage of research is conducted, the overhead from research is one of the few funding streams that remain for the cross subsidies of care. As federal and private insurance tighten reimbursement, medical centers that responsibly pursue care for the uninsured and the underinsured have fewer avenues to explore. Overhead is one. One could argue that ethically, and perhaps even legally, the monies generated by the overhead of research must first be used to conduct ethically adequate research.

IV. REDRESSING THE VAST VARIATION IN STANDARDS THAT GOVERN RESEARCH WITH THOSE WHO CANNOT PROVIDE LEGALLY AND ETHICALLY ADEQUATE INFORMED CONSENT

A federal regulation provides that the legally effective informed consent of the prospective subject, or the subject's legally authorized representative, is a prerequisite for enrolling the subject into a research protocol.¹³ The regulation definitions refer the IRB to state law in order to answer the question of who might be the possible consentor for the subject if there is question regarding the subject's capacity or understanding. Needless to say, there are major differences among state approaches to this question of substituted or surrogate consent; within each state, there are major variations in the policy and protocols followed by different IRBs.

Consider the following: A geriatric physician decides to evaluate which of the present regimens for providing analgesia is most effective for controlling the pain of debriding (removing the dead tissue) decubidae (bedsores) when the procedure is done in the hospital at bedside. None of the various ointments and analgesics currently used have been tested in clinical trials, so no quality data exist as to relative efficacy. Most of the potential subjects are patients transferred from nursing homes and are somewhat-to-totally demented. The IRB is likely to give the investigator and sponsor any one of the following statements:

1. You cannot embark upon this research unless each patient has a guardian appointed by the court;
2. You cannot enroll a patient unless the patient, when capable, executed a durable power of attorney for health care decisions with a specific provision that permits entering the patient into research trials after incapacity has intervened;

¹³ 45 C.F.R. § 46.116 (2002).

3. You can only enroll patients in the trial who have the capacity to provide legally and ethically adequate consent;

4. You can ask the patient's closest relative and if that person, who consents for the patient's care in general, gives permission, you may enroll the patient.

What determines which one of the above answers is provided depends on the luck of the sponsor, the visibility and applicability of provisions of state law in this arena, and the sophistication of the IRB. More guidance is needed. And what if the protocol is not in the rather open, collegial, and penetrable setting of the hospital, but is instead a protocol conducted in the private office? What if the trial is to see which of the developing drugs for Alzheimer's disease is most effective? The need is great, the effective alternatives few, the concern of caregivers high, and the vulnerability of patients extreme. Those should not be situations in which the IRB permits the office-based practitioner the opportunity and authority to reach conclusions about the capacity of the appropriate consentor. The further the research is located from open scrutiny, the more it needs to be grounded in clear rules that both permit research and protect vulnerable populations.

V. ENHANCING THE ETHICAL SENSIBILITY OF THE RESEARCH COMMUNITY

Big money is good news and bad. In the decades after the Second World War, as the budgets for medical research supported by the NIH expanded, researchers scrambled for those funds to support their interests, enhance their reputations, and provide the basis for academic advancements and rewards. These were politely referred to as the "incentives" for research, but they established platforms for competition, success, and failure. As the rewards for research reach new financial heights, we need to return to Hans Jonas and ask: What are we as a society gaining? And what new dangers appear in these new configurations? In my judgment, one stands out prominently: the danger that researchers will come to see themselves as "piece work" employees rather than as collaborating scholars in the research endeavor. Those who work by the hour or by the task rarely engage in the business of questioning the entire enterprise—is it asking the right questions, collecting the most appropriate data, and publishing the most helpful and fair-minded reviews of results? Is the research enterprise acting morally to serve the health needs of the sick? Has it set its agendas to maximize the greatest goods for the most people?

Is it acting responsibly in the face of competing interests? These are not questions that private practitioners in the comfort of their isolated offices will formulate or pose to research sponsors. Their responsibility is to follow the protocol and deliver the data. That is, I fear, too narrowly defined a task.

Research is always ethically “dicey,” to quote my colleague David Rothman, as it uses subjects for the benefit of knowledge and subverts the judgments of clinicians to the requirements of the protocol. Yet it is the only way that we can develop evidence-based medical knowledge that reflects reality rather than the experience of only one or two physicians. Research is increasingly important to a population that demands an increasing lifespan and a higher quality of life. But doing it well and responsibly requires critical examination, review of the process, and a robust discussion among scholars both inside and outside of the industry regarding goals of designs and the safeguards for participants.