Trust

The Fragile Foundation of Contemporary Biomedical Research

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It is widely assumed that informing prospective subjects about the risks and possible benefits of research not only protects their rights as autonomous decisionmakers, but also empowers them to protect their own interests. Yet interviews with patient-subjects conducted under the auspices of the Advisory Committee on Human Radiation Experiments suggest this is not always the case. Patient-subjects often trust their physician to guide them through decisions on research participation. Clinicians, investigators, and IRBs must assure that such trust is not misplaced.

In addition to its investigation of research conducted in the past, the Advisory Committee on Human Radiation Experiments also examined the current status of research with human subjects to ensure that research today and in the future be conducted in accord with the highest ethical standards. To that end, the Advisory Committee conducted three projects that examined *contemporary* human subjects research. Among these was the Subject Interview Study, a project that enrolled almost 1,900 outpatients nationwide to determine their experiences with and attitudes about research.[1] Approximately one hundred of the patients who enrolled in this study and reported having personal experience in medical research were interviewed a second time and in greater depth to gain further insight into their reasons for participating and their understanding of the research enterprise. This paper describes the findings from these interviews and their implications for conducting ethically sound research with human subjects.

These in-depth interviews were conducted at fourteen institutions across the country, including academic research institutions, Veterans' Affairs hospitals, community hospitals, and federal government hospitals. Patients were recruited from the waiting rooms of medical oncology, radiation oncology, and cardiology outpatient clinics at each of the participating institutions. During interviews, which averaged forty-five minutes, patients were asked to describe the research project in which they were enrolled, how they had learned about it, how they had decided to participate, consent procedures, how they felt about the experience, and how they felt about research more broadly. Interviewers encouraged respondents to speak freely about each topic and also to raise additional topics that were of relevance to their experience in medical research.[2]

Of the 103 patients who were interviewed, there were almost equal numbers of women and men. Patients tended to be Caucasian (74%), to be high school but not college graduates (52%), and to have private health insurance (65%). Participants also were significantly more likely to be in research evaluating a therapy (65%), than in survey research or studies evaluating a diagnostic test. In this report, we will focus predominantly on the experiences of patients enrolled in therapeutic research.

Why Patients Become Subjects

Many factors influenced patients' decisions to participate in research. And as one might expect, those in therapeutic research cited different reasons for participating than did those in other types of research. Among the more prominent motivations for subjects enrolled in therapeutic research was a sense that the experimental intervention was better than any existing alternative, and indeed offered some hope of personal benefit.[3] Patients made comments such as, "If there's something new on the market that might be better than the traditional program they've been using, why not try it?" (Subject 333208-7), or "I was more interested in something more advanced and potentially better" (443247-2).

The theme of hope was often wedded to despair. For many patients, research came after they had tried other standard or experimental interventions and either had exhausted those treatments' effectiveness or had experienced little benefit at all. Often, they viewed the investigational "treatment" as a last hope for improvement or amelioration of their conditions. As one respondent said, "Well, what was driving me to say 'yes' was the hope that this drug would work . . . When you reach that stage . . . and somebody offered that something

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that could probably save you, you sort of make a grab of it, and that's what I did" (332250-0). Less typical were the comments of one respondent who said, thoughtfully, "You don't know what that cancer's gonna do. God, I don't . . . think anybody can guarantee you any benefits" (552126-5). Clearly, many patient-subjects hope for personal benefit when they enroll in research, hope that this intervention might offer them longer life, less pain, or fewer symptoms.

Yet many participants who had tried other interventions without success felt more that there simply were no alternatives left. They characterized the decision to participate as a matter of little choice: "My doctor told me if I do not take the drug, in a couple of months I [will] die. So, I had no choice. Who wants to die? Nobody" (333215-2). Similarly, one patient said, "Well, he [the oncologist] said he'd already been through everything he knew what to do. He would try to keep me as comfortable as he could. That's when he told me about this new treatment. I told him we would try it" (443250-6). One respondent said, "They didn't pressure me, but I felt pressure because there isn't anything else" (334110-4).

Physicians' recommendations were also powerful factors influencing patients' decisions to become research subjects. The comments of two respondents are typical: "My personal reasons [for enrolling] were because I was advised to do it" (335227-5); and, "He asked me if I wanted to go on it, and I said 'If it's what you think I should do, yes, because you know more about it than I do.' . . . [H]e said, 'I think it would be a good idea to try it'" (552264-4).

Such reflexive decisionmaking regarding research is indicative of the immense trust that patients placed in their physicians; participating in research was simply the right thing to do if their doctor recommended it. "There's not a lot that you can control when you're sick, so you have to rely on your doctors . . . if he suggests that you should go into a research project, I think you should really take his advice or her advice . . . because if you take the time to get yourself a good doctor and they're involved in research, they would never steer you wrong" (552244-6). Perhaps the most extreme comment along these lines was from a respondent who described her doctor's role in her decision to participate, "Oh, I love that man. He has kept me alive and I obey him and I do what he tells me to do" (114217-3).

Patients also placed a good deal of trust in the hospitals in which they were receiving care. Their belief was that if you come to the right place, you get whatever is the best available treatment. You can *trust* that if they're conducting this research at that hospital, it must be state-of-the-art. "I think I've got the best treatment down there at [named hospital]. I don't think I could get any better" (333208-7). Similarly, "If it's not through [named hospital], I wouldn't touch it" (442304-2).

Finally, respondents expressed trust in the research enterprise as a whole. There seemed to be a widespread belief that checks and balances were in place, and oversight ensured that no harms could be done. For instance, one respondent said, "They know what they're doing. They wouldn't have you do this if they didn't know what they were doing" (332324-3); and "I do not feel like the drug would be on the market if it were going to harm me, and if it would help in any way . . . I'm very willing to participate in this and perhaps other studies" (443241-5). Perhaps the most blatant expression of this trust was the patient who said, "I don't believe they would offer me anything that isn't beneficial to me, in my condition" (221106-8). Much more unusual was a patient who believed he should be more in charge of his own treatment decisions: "I sort of take my own treatment in my head and tell them that I'm his client. It's not the other way around" (552143-0).

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Comments about the consent process underscored the importance of trust in the experiences of these patients. Many participants expressed that their decision to participate had been made before they had been given the consent form to sign. They knew they wanted to participate, they trusted that it was right, and the details described in the form were not particularly relevant. "[T]o me, they are the doctors, and once I had gotten those doctors and I trusted them . . . it was pretty much up to them. I wanted to know what I was going to be going through as far as what to expect . . . but a lot of the little nitty-gritty detail, I did not even want to know" (114250-4). Even those who tried to understand what they were being given to read about the study expressed a similar feeling: "I read some of the literature and it didn't mean a hill of beans to me because I didn't know anything about medical science but, like I say, if it's to help me, I'll go in" (332324-3). Patients assumed that they need not pay attention to what was written in a consent form, or suggested that although the form was not particularly readable, it did not matter because they knew they wanted to participate in research regardless.

This belief seems to hinder the adequate fulfillment of the informed consent process, however. The comment by one patient-subject that when offered the possibility of being in a medical research project, "you make a grab for it" is quite revealing. The stories these patient-subjects told about why they decided to participate in research suggest that the current

emphasis in research ethics on analyses of benefits and risks and on subjects' autonomous decisionmaking is insufficient. The paradigm must be enriched with a sensitivity to the profound trust participants place in researchers and the research enterprise.

The Significance of Trust

The concept of trust has been addressed in the literature in reference to the physician-patient relationship both generally,[4] and in the specific context of research.[5] Edmund Pellegrino suggests that trust is essential to all human relationships and functions to reduce complexity.[6] On Pellegrino's view, a climate of mistrust—that might ensue if violations of trust are experienced—cannot sustain itself. He notes, "We must trust that our vulnerability will not be exploited for power, profit, prestige, or pleasure" (p. 73). He also claims that patients only should entrust to doctors that piece of their "good" that is medical:

> Medical good is only one of the components of the complex notion of patient good . . . patients should not entrust to the physician the responsibility for determining the totality of their good, [and] physicians must not assume they are entrusted with such a broad mandate. (pp. 80-82)

This is particularly relevant in the research context since there are many nonmedical consequences to being in research. Changes in quality of life, interference with work or home life, and demands on a patient's time all can contribute to what constitutes the patient's overall "good."

Annette Baier asserts that when trust exists, harm as well as good can result: "Not all the things that thrive when there is trust between people . . . are things that should be encouraged to thrive . . . There are immoral as well as moral trust relationships."[7] To the extent that patients' vulnerabilities are taken advantage of in research—even as a result of well-intentioned inaccuracies in descriptions of the research or exaggeration of the likelihood of benefit—the boundary into an "immoral" trust relationship has been crossed.

Investigators face extraordinary challenges in maintaining their integrity. If desperate patients come in search of help, and an investigational intervention is available that is targeted for their condition, it is very difficult to present information about the risk and value of that intervention without in some way stimulating patients' hope. Yet there is a morally critical fine line between allowing or even encouraging a patient's hope because of the beneficial value hope itself can provide and misleading the patient to a point where hope is raised inappropriately and harms are created.

Respecting this line necessitates understanding the difficulties in distinguishing medical research from treatment. For many of the patients interviewed in this project, medical research and medical treatment were closely connected. On the one hand, respondents seemed to be quite capable of distinguishing which interventions were associated with the research, separate from their regular clinical care. Similarly, they were clear in pointing out what the unique goals of a research intervention are, asserting, for example, that "[Research is] the only way advancement is made in the medical field . . . [I]t's gotta be done at some point in time on human beings" (551334-6). Such statements suggest that respondents recognize that the goal of research is to help society broadly, while the goal of medical care is to advance the best interests of the individual patient.

Through further discussion, however, it was evident that most respondents, while able to articulate the broad goals of research, viewed their own participation as simply another treatment option. One respondent, when asked to describe her research experience, replied, "I think of it as a means of treating what I have" (335227-5). Another's comments suggested a similar belief, "[participating in research] was through necessity . . . The thought never entered my mind that I would withdraw from this program" (553215-5).

Such results ought not to be surprising perhaps, given the documented tendency of some physicians to inflate the potential benefits of research interventions. In one study, virtually all physicians thought their patients would benefit from investigational treatments, and 43 percent said they had "no doubts at all about benefits of treatment" despite a statement in the consent form that benefit could not be assured.[8] In another study, physicians consistently overestimated the likelihood of benefit from clinical trials.[9]

Nevertheless, altruism clearly also played a role in respondents' decisions to participate. Although for some altruism seemed to be their primary motivator, for most others it was just a component of their overall decision. For example, some respondents conveyed that while they were hoping for personal benefit, it could not be guaranteed, and that at least good would come to someone else as a result of their having participated. As one remarked, "I was hoping, if not for me, at least something for the next people coming along" (223212-2). Another respondent who had a hereditary condition was quite deliberate in wanting to join an effort that might help others in the future:

> because if it's hereditary and it sure seems [to be] in my situation . . . I'm concerned about my daughter. I'm concerned about her kids, and [it] goes on and on and on . . . [W]ithin my generation I've had three cousins die of the same thing (221240-5).

Another respondent indicated that her own approach to research had changed as her illness had progressed:

> [I]t will never cure me . . . I'll be dead in the next couple of years . . . but if they can find something that can save someone else [I'll be happy] . . . I don't have the expectations that . . . I did . . . seven or eight years ago . . . I'm realistic. It might help. It might not. But, you know, they're going to find out something that's going . . . to help somebody else and you have to think of it that way (335213-5).

Still others viewed participation as almost a civic responsibility. "I feel like [participating in research] is a moral obligation as a citizen. You put back into your community" (443218-3).

Not surprisingly then, patients conceptualize research participation in quite complex ways. On the one hand, patients described themselves as sincerely motivated to help others, while, on the other, they suggested that they would not have participated on that basis alone. Most patients were aware of the broader stated purpose of research and could discuss research as an endeavor that advances science and helps future patients; yet patients also expressed that they would not have joined if they had not believed that some personal benefit might result as well.

Clinicians should be mindful of the tremendous influence they have over their patients, given that the mere suggestion of enrollment in research by a patient's personal physician was interpreted by many patients to be an endorsement.

Implications for the Conduct of Research

These findings have significant implications for individual clinicians, investigators, and those who evaluate and regulate clinical research. Clinicians should be mindful of the tremendous influence they have over their patients, given that the mere suggestion of enrollment in research by a patient's personal physician was interpreted by many patients to be an endorsement. This is not to suggest that, absent certainty (which obviously is an impossibility), physicians should not offer patients options, including research participation; but physicians should be sensitive to the extraordinary power of their remarks. If research is one in a series of options for a patient, and research offers a possibility of benefit, but a minuscule one given existing evidence, then that intervention should be described in a manner that is consonant with a realistic portrayal of these risks and benefits. That is, research should not be presented simply as a new intervention with possibilities for beneficial effects, but as an intervention with little evidence suggesting whether effects will be beneficial or harmful. In the end, physicians, even with the best of intentions, do their patients a disservice if they are inaccurate in their portrayal of what it means to be a subject of research.

Investigators, on the other hand, should make it clear that their primary loyalty is to future patients. While investigators also unequivocally have an obligation to minimize harm to subjects and to respect their wishes, patients who enroll as research subjects must understand this shift in loyalties that is inherent to the role of investigators, in contrast to that of patients' personal physicians.

So too those who oversee research should be humbled by the trust patient-subjects have in the research enterprise and should continue to do their best to live up to that trust. The findings of the Subject Interview Study are a cogent reminder for institutional review boards (IRBs) to take seriously their responsibility to review research on subjects' behalf, and not to allow research to be approved with the assumption that patient autonomy and informed consent will provide sufficient protection. Patients assume that research into which they enter is safe, trusting that the research enterprise protects them from harm. They often do not read consent forms carefully because they assume that someone else has scrutinized the risks and benefits on their behalf. These findings suggest that a paternalistic stance of IRBs not only is warranted, but is expected.

IRBs should also take measures to assure that investigators do not overrepresent the benefits of research and that all consequences of the research that relate to the patient's "good" be explained. For example, when reviewing consent forms for Phase I research, IRBs should strike out comments suggesting the likelihood of personal benefit to participants. Such actions send a clear message to investigators, and those potential participants who choose to read these forms, about the investigative nature of such trials. Similarly, IRBs should assure that potential subjects are provided with information about the duration of the trial, any associated discomforts, and information concerning how the trial could affect their ability to function in daily life.

It is essential to recognize that the trust which patient-subjects place in their physicians and the research enterprise is likely to be quite fragile. As Sissela Bok has written, "It is far harder to regain trust, once lost, than to squander it in the first place."[10] Examples from the past highlight that abuses of human subjects have a lasting and devastating effect not only on individuals' trust of biomedical research, but also on entire communities.[11]

Human subjects research allows scientific and medical progress to move forward, which is in the best interests of all of us. To be entrusted with the authority to conduct human subjects research is a privilege. Yet only through vigilance and humility will we as investigators be able to live up to the trust that is placed in us; and only if that trust is deserved can the research enterprise survive.

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References

1. This study is described in detail in Chapter 16 of the *Final Report of the Advisory Committee on Human Radiation Experiments* (Washington, D.C.: U.S. Government Printing Office, 1995), pp. 724-57.

2. Interviews were audiotaped, transcribed, and analyzed using qualitative techniques and text analysis computer software. Copies of all transcripts and TALLY analysis segments are available through the records collection of the Advisory Committee on Human Radiation Experiments maintained at the National Archives and Records Center, Washington, D.C. Quotations from interviews presented in this article are identified by subject number in the text.

3. Similar findings have been reported from other studies, for example, Barrie R. Cassileth et al., "Attitudes Toward Clinical Trials Among Patients and the Public," *JAMA* 248, no. 8 (1982): 968-70; Sjoerd Rodenhuis et al., "Patient Motivation and Informed Consent in a Phase I Study of an Anticancer Agent," *European Journal of Cancer and Clinical Oncology* 20, no. 4 (1984): pp. 457-62; Christopher Daugherty et al., "Perceptions of Cancer Patients and Their Physicians Involved in Phase I Trials," *Journal of Clinical Oncology* 13, no. 5 (1995): 1062-72.

4. See, for example, Richard M. Zaner, "Phenomenon of Trust and the Patient-Physician Relationship," in *Ethics, Trust, and the Professions: Philosophical and Cultural Aspects,* ed. Edmund D. Pellegrino, Robert M. Veatch, and John P. Langan (Washington D.C.: Georgetown University Press, 1991), pp. 45-63; Joseph P. Lyons, "The Doctor in the Current Milieu," *Perspectives in Biology and Medicine* 37, no. 3 (1994): 442-59; Annette Baier, "Trust and Antitrust," *Ethics* 96 (January 1986): 231-60.

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7. Baier, "Trust and Antitrust," pp. 231-32.

8. Doris Penman et al., "Informed Consent for Investigational Chemotherapy: Patients' and Physicians' Perceptions," *Journal of Clinical Oncology* 2, no. 7 (1984): 849-55.

9. Sudha Rajagopal, Phyllis J. Goodman, and Ian F. Tannock, "Adjuvant Chemotherapy for Breast Cancer: Discordance Between Physicians' Perception of Benefit and the Results of Clinical Trials," *Journal of Clinical Oncology* 12, no. 6 (1994): 1296-1304.

10. Bok, "Shading the Truth," p. 11.

11. James H. Jones, "The Tuskegee Legacy: AIDS and the Black Community," *Hastings Center Report* 22, no. 6 (1992): 38-40.