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The Rights of Patients to Participate in Clinical Research

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RESEARCH: PROCESS AND PURPOSE

In the West, we trace the beginning of clinical research to Dr. James Lind, who in 1747 studied six treatments for scurvy on twelve sailors aboard the HMS Salisbury as it sailed from England to Plymouth Colony.[1] The study lacked the rigor of modern clinical trials, but it was the first recorded Western instance of a documented scientific approach comparing the effects of interventions in humans.

Modern clinical research is more sophisticated than this early example, but it has the same purpose – *prospective* studies comparing the effect and value of an intervention against a control in human beings,[2] requiring that an intervention be planned and applied *selectively* in humans to determine its impact. When properly planned and conducted, clinical trials assess the effectiveness of care and enhance treatment armamentaria.[3] By comparing alternatives, clinical research has great potential to save lives, improve the quality of life, reform healthcare, and control costs.[4] It is from these comparisons that conclusions are drawn about the value of an intervention.

PATIENT PARTICIPATION: IMPERATIVES AND DEMANDS

Patient participation is no small matter in today's healthcare systems, which treat both newly emerging communicable diseases and increasingly complex combinations of chronic and acute conditions afflicting young and old alike. Researchers need patients who are willing to participate in the studies that will generate answers to the questions of

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how to treat conditions effectively and efficiently, returning the patients to high-quality lives with good clinical outcomes at the lowest possible cost.

When clinical studies began in modern-era American healthcare, human research subjects were drawn from pools of patients within this country who were seeking access to the best medical care. Research endeavors were small at first and were funded privately by philanthropists supporting individual researchers. Beginning in the 1950s, increases in federal funding initiated the development of a larger, more complex infrastructure for conducting greater numbers of clinical studies, which thus created the need for even more research subjects. Researchers turned to institutions housing large numbers of accessible individuals: prisons, schools for the retarded, and the military. By the 1960s, the clinical research enterprise had developed even more and the demand for research subjects increased even further as Food, Drug and Cosmetic Act legislation required that drugs on the market be researched to ensure that they were safe and effective. Researchers not only improved the scientific methods of clinical research during this era, but also dramatically increased the number of research studies, creating even greater demand in the number of research subjects required for the development of new medicines.

The growth in both the number of research studies being conducted and the number of research subjects needed to fill them continues to accelerate. Pharmaceutical companies now predict a 65 percent increase in new compounds emerging from their labs.[5] Over 90,000 clinical trials are currently under way in the private and public sectors, 80 percent of which are not meeting enrollment deadlines for patients. Just over 25 percent of clinical development time is spent identifying and enrolling subjects, and though it spends an estimated $1 billion annually to recruit patients,[6] the pharmaceutical industry incurs losses of up to $1.3 million per day due to trials uncompleted because of enrollment difficulties in the United States alone. Even the U.S. government, for its own clinical research, has been required to develop Web-based communications to attract patients to research trials.[7] Researchers now also travel abroad for human subjects, searching particularly in developing nations. The number of foreign clinical investigations grew sixteenfold between 1990 and 2000, and the number

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of countries in which clinical trials were conducted grew from 28 to 79 during the same period.[8] Securing sufficient numbers of clinical trial subjects for this most basic participatory role is not a trivial concern.

PATIENT PARTICIPATION: MATURATION AND RECOGNITION

In the past, the goals, methods, mechanisms, and patient recruitment aspects of clinical research were the prerogative of scientists and regulators. Increasingly, however, patients are demanding the right to participate in all of these aspects of the clinical research process. Researchers, regulators, and policy officials should be asking and answering pertinent questions about this movement toward collaboration: Why would patients demand greater involvement in research? Should patients be granted this right? How will clinical investigations be impacted if patients have a right to participate not only in trials but in the determination of who will be studied, what will be studied, and how it will be studied? Will this result in a setback for research, or catalyze a giant leap forward? What changes will be required as patients become more knowledgeable about and active in the research process? Will patient participation help or hinder the development of new knowledge and innovative medicines? What are the dynamics at play in these new demands from patients and their advocates? What is the nature of the collaborations they seek? Is this an indication that we have failed them in some way?

Currently, it is patients, not researchers or regulators, who are leading the way in redefining patient roles by becoming more active in developing research agendas, determining research designs, and gaining access to trials themselves. This empowered "patient rights" movement comes late to the research ventures of healthcare. It trails behind the demand for rights to privacy, access, affordability, and quality, but it has come knocking at the research door nonetheless. In fact, the demands for collaborations in research should come as no surprise, as they are consistent with the evolving state of the physician-patient alliance. It is time for researchers to respond as clinicians have and welcome patients to a more mature partnership. Just as patients are becoming partners in the care they receive, now, too, they are also seeking similar partnerships in research.

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In a very real way, however, it is not the *fact of participation* that is new, but the demand for *more comprehensive involvement* in the research enterprise and for *recognition of the influence* patients already have in research. It would be unwise to ignore these new patient demands and to fail to recognize the comprehensive contributions of patients. Patients have not only participated as human research subjects, but for many years they have been involved in clinical research in other ways as well. They have been active in private-sector fund-raising for research and have created organizations to support researchers in academia and the private laboratories. They have been active in public policy, lobbying for research training and clinical trial funding from governments. They have supported legislation promoting intellectual property protections and have argued successfully for access to new therapies. In recent years, they have contributed to our understanding of how to recruit human subjects into trials, increased our understanding of cultural sensitivities needed to conduct research among minority and certain disease groups, and argued successfully for expedited regulatory review of important products. It is not the *fact* of the participation that requires exploration, but the *nature* of that participation today. It is not the *reality* of participation, but the conscious *recognition* of participation that is a new imperative in the modern pursuit of innovation.

These matters are the subject of this chapter. I intend to address several of the critical issues that currently drive newly empowered patients to demand the right to participate in research in new ways, note the growing need for collaboration with those who are the subjects of research, and argue that patients can be effective partners in the development of new knowledge. This is not a new or radical idea – patients have long been partners. It is time we in biomedical research recognize their contributions and honor their willingness to assume more visible, integral roles. But how? What are the next steps we must take? I believe there are three fundamental tasks at the outset. If we fail to succeed in these, all of our efforts to engage in mature partnerships will likely fail. First, we must restore trust in researchers. Second, we must embrace those patients who are at the leading edge of patient demands. Third, we must return to our roots in medicine and recognize that a failure to accommodate patient demands is a failure to live within the oaths we have taken as healers.

RESTORING TRUST IN RESEARCHERS

Ensuring the ethical treatment of patients who participate in trials is neither trivial nor easy. Even the twentieth century – a time most people would have called "civilized" – produced examples of egregious behavior in clinical research, including dangerous and harmful experiments performed on nonconsenting patients.

In the worst cases, experiments were performed on institutionalized individuals, the poor, or groups regarded as "lesser humans," including Jews and others in Nazi concentration camps, the mentally retarded, prisoners, persons of African descent in America, and indigent patients. Often, these individuals were unable to decline to participate in the research study,[9] either because their consent was not sought or because a physician fraudulently described the experiment as a diagnostic procedure or treatment for the patient's condition.

In 1963, for example, American researchers injected live cancer cells into elderly debilitated patients in a Jewish chronic disease hospital.[10] In the same year, intellectually disabled children were injected with hepatitis in a New York State public institution.[11] For forty years, beginning in 1932, nearly 400 African American men in the Tuskegee study of syphilis were left untreated – and were actively discouraged from seeking appropriate care – as part of a study designed to observe the natural course of untreated syphilis. It was not until 1965 – nearly twenty years after penicillin was demonstrated to be effective against the disease – that clinicians objected to the experiment on ethical grounds and not until 1972 that the Associated Press (AP) was tipped off and released the story.[12]

In other studies, prisoners were subjected to malaria, typhoid, and cholera.[13] In an earlier example from the nineteenth century a gynecological surgeon in the southern United States demonstrating a profound lack of compassion conducted surgical experiments on African American women without anesthesia, believing that they did not suffer and would "bear pain" better than white women.[14] Patients today may be unaware of the details of these atrocities, but they are not unfamiliar with the reality of major ethical breaches.

Modern research ethics came about largely because of these revelations. The global community responded, calling the Nazi experiments crimes and crafting the Nuremberg Code, the first international

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normative framework to regulate standards in clinical research trials.[15] This document was superseded by the Declaration of Helsinki, a code for research and experimentation that was endorsed by the World Medical Association (WMA) in 1964 (Juhanna Idänpään-Heikkilä and Sev Fluss offer additional information on the history of international ethical codes in Chapter 2).

Nonetheless, ethical lapses have continued, even recently and in situations in which regulatory bodies exist to ensure patient protection. In New Zealand, for example, a hospital ethics committee and Institutional Review Board (IRB), both charged with protecting human research subjects, approved a study that denied treatment to women with cervical cancer, failing to tell them of the diagnosis or of the research study, though they were repeatedly brought back to the hospital for observation. Many died when timely knowledge and treatment could have saved their lives.[16]

Understandably, patients and advocates familiar with ethical misconduct are much less likely than others to be willing to participate in studies.[17] This should surprise no one in the research enterprise. Everyone involved – from researchers to regulators – should know that regardless of the good intentions of particular studies, or the high standards of adherence for most studies, all studies bear the burden of eroded trust created by these lapses in ethics. Today's empowered patients cannot be expected to willingly enter trials in the face of difficult-to-ignore ethical violations. There are many good reasons to offer patients a "seat at the table," but none is better than to initiate the transparency that will reassure them that researchers are doing their best, especially in situations where ethical issues are unclear and uncharted, to protect human research subjects. Opening the doors to previously closed discussions about clinical trial design and research methods will help to restore trust in the research process.

Unfortunately, past breaches of trust are only some of the barriers to earning the trust of today's patients. Other concerns include researchers' conflicts of interest, "finder's fees" paid to clinicians who refer patients to clinical trials, drug-pricing policies that put drugs out of reach of many who helped to develop them, and the lack of transparency of research results. These, too, are concerns that must be addressed if researchers expect trust from those who must willingly place themselves at risk as subjects of medical experiments.

Only by involving patients will it be possible to navigate these and other increasingly complex ethical waters that lie ahead in clinical research. Consider the evolving ethical and technical aspects of human subjects research. Some of the emerging ethical challenges into which patients can provide invaluable insight are cultural. In some countries, for example, individual consent on many matters important to life is not a commonly held value, and the notion of individual consent in research is quite foreign. In those countries, it is acceptable for consent to be granted by the community of the whole, by tribal leaders, or by some other person, such as the husband of a female subject.[18] The age of majority also varies around the world. In the United States, the legal age for consent is 18, but in many other countries it is much younger. Research conducted in those countries, and research on immigrants arriving from those nations, must be approached with sensitivity to these cultural practices, widely divergent as they may be from those in the United States.

Others of these ethical challenges are technical. Even though informed consent is legally viewed as a *process* rather than a *document*, the process is usually accompanied by a document that is signed by those involved. As Dr. Valentine Burroughs notes in Chapter 5, this can be problematic among those with low literacy[19] or in the case of immigrants from countries where citizens fear that signing a document may place them or their families at risk of reprisals from an oppressive government.[20] Informed consent is also problematic in countries where the language has no words for "research study."[21] In some cultures, research subjects' belief systems about science, health, and disease are so divergent from those of Western nations that the nature of the research intervention cannot be explained accurately.[22,23] Further complicating the technical challenges, requiring the name and telephone number of a research contact is impossible among poor or highly mobile groups where people do not have telephones or consistent contact information. At long last, these patient-centered research participation considerations – which go beyond those of informed consent – are being addressed by ethicists who are working to evolve ethical requirements for clinical research. They will be addressed successfully only if those from the affected communities are involved to ensure that their unique issues of importance are accommodated.

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At the cutting edge of these new relationships, patient advocates are showing us the way to build and maintain their trust. Their demands go beyond informed consent and fair treatment as human subjects to the heart of research itself. They want, for example, studies to be conducted in scientifically valid ways in order to ensure that scarce financial and human resources are not allocated to projects that are unlikely to benefit humanity. They demand social justice in research, ensuring that subjects are selected in ways that are fair and do not stigmatize, or make vulnerable, someone who participates in a study. They want assurances that the poor and powerless should not be chosen for more risky (or less beneficial) research, whereas the rich and powerful are chosen for less risky (or more beneficial) studies. They suggest independent reviews of research to ensure public accountability and prevent potential conflicts of interest. Finally, in addition to informed consent, they believe that, out of respect for human subjects, all research subjects should be informed of the study results and of any negative outcomes of studies. To some in research, these might seem unreasonable intrusions. However, these are the steps that must be taken to ensure that patients have our trust and are willing, therefore, to continue to participate in the research ventures they have so long supported.

EMBRACING PATIENT DEMANDS

In Chapter 17 of this book, Martin Delaney includes a detailed discussion of the history of the AIDS patients' movement. There is no better, clearer contemporary example of patient leadership. The experience with AIDS patient advocates should inform all efforts to address patient needs today. It is precisely this type of leadership – at the cutting edge of patient demands – that we should embrace as the research enterprise grows and matures in the future. The appearance of empowered patients, triggered by HIV/AIDS in the 1980s, might seem to some to have been a threat to research. In fact, this new movement of patient involvement was an opportunity, and one we have not yet fully embraced within biomedical research, particularly with regard to other conditions.

As the virus took hold and the search for therapies progressed, the HIV/AIDS community influenced the nature of clinical study

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participation, creating a research-subject empowerment movement and the first highly successful patient-driven demand for research participation. AIDS patients became more influential in the conduct of research than any group before them. Facing social stigma, cultural bias, and certain death, they empowered themselves and forced change. They demanded that they be allowed to participate in the development of research priorities and the design of protocols and, as research subjects, even tested their experimental compounds in laboratories – a clear violation of research "blinding." Their activist demands to participate in research led to studies that accrued patients more quickly, addressed community-based concerns more successfully, and contributed to the development of current therapeutic regimens that have altered the life courses of those HIV-positive individuals.

The HIV/AIDS crisis also heightened awareness of the ethnic, gender and racial diversity of persons living with the disease. No longer was it acceptable to draw clinical trial subjects exclusively from groups of white, middle-class men. As it became increasingly clear that medicines had different effects on different groups of patients, the need for larger and substantially more diverse groups of patients in studies was recognized. As a result, investigators and regulators alike now seek a better balance of gender, racial, ethnic, and age groups in clinical trials to ensure that all groups of patients will be fairly represented and that the action of the medication in subpopulations of patients will be understood (this is also addressed in Chapter 5 by Dr. Burroughs). The recognition of patient diversity brings thrilling new ideas to medicinal innovations and increases the opportunities for better targeting of effective therapies. Unfortunately, it also brings the single greatest challenge to the researcher-subject relationship; that is, the need to develop new skills to reach out to increasingly diverse human subject populations. These skills are essential, given that the changes set in motion by HIV/AIDS activists have been adopted by women living with breast cancer, those living with hemophilia, and other vocal patient advocates addressing the unmet needs of their constituencies.

It was during the early AIDS research era that the most vocal patient advocates argued that participation is more than a *goal*. They argued that participation is a *right*. What type of right? The right to participate as a subject in a trial, the right to participate in the design of a clinical trial protocol, the right to participate in trials themselves, and the right

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to have a voice in the research enterprise overall. I propose that patients and their advocates have a right to participate in the planning, design, and conduct of clinical research by virtue of their historical willingness to participate as subjects and supporters of the research ventures I have already described here. I also suggest, however, that they have earned this right by virtue of their evolving skills within this arena. As patients and their advocacy organizations today are more capable of being mature partners with clinicians during the process of care, so, too, are they capable of being more mature partners with researchers during the process of knowledge development.

Once passionate but somewhat unprofessional, many patient groups today are highly professional, organized, well-capitalized, competent collaborators. They are knowledgeable about disease conditions, medications, and life-style issues and are trusted communicators within their networks of patients and clinicians. They have sought, and heeded, the advice of scientists and clinicians and are articulate spokespersons for those they represent. They are effective in recruiting patients for clinical trials, particularly in situations where special disease, gender, racial, or ethnic community concerns slow patient enrollment, and they are sought out by regulators during the drug-approval process and in times when crises arise in the use of medications.

Medical advances since the beginning of modern biomedical research have extended the life span, reduced morbidity, and improved the quality of life globally. This happened because patients were willing to participate. There is little doubt that the support of patients and their advocates will continue to be required to design trials, to recruit patients, to fund research, and to ensure that innovations are widely available. Research will continue to require human subjects in order to continue to make progress in addressing the prevalent and emerging diseases of the world. We owe a great debt to those professionals who advance medical technology and science. However, any progress in acquiring new knowledge depends on the willingness of those individuals who risk pain, disability, and even death as research subjects. We owe a great debt to them as well.

It would be unfortunate to ignore the even greater contributions that patients and their advocates can now make to the progress of science. The time has come to accept and acknowledge their role and potential by granting them access to participation not only as subjects, but as true

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partners in mature, comprehensive relationships in research. We'll all be the better for it. But is that enough?

LIVING OUR OATHS

Epidemiology and population-based studies, computer simulations, and *in vitro* studies yield insights about health and disease. Eventually, however, human studies are necessary to tease the mysteries from the body. It may well be a messy business to deal with empowered patients who hold divergent views about research. Some will fear the motives (including the profit motives) of investigators, or may distrust institutional review boards. Others will have access to medical care close to home and be unwilling to travel to research centers. Still others will hold diverse cultural notions of disease or ethnic biases about research. Nonetheless, cooperation with patients is necessary and will both improve the nature of the investigative process and ultimately hasten the development of the knowledge we all seek. Failure to cooperate will hamper the progress we all envision.

In fact, those involved in the healing enterprise have little choice in the matter. The solemn oaths they take as healers require not only that they care for patients, but also that they seek new knowledge about the human body, health, and disease. The Oath of Hippocrates included research by implication in this commitment to learning and teaching, swearing

> To consider dear to me as my parents him who taught me this art . . . to look upon his children as my own brothers, to teach them this art if they so desire. . . .[24]

The oath developed by the twelfth-century Jewish sage Maimonides was considerably more explicit:

> Thou hast granted man the wisdom to unravel the secrets of his body, to recognize order and disorder; to draw the substances from their sources, to seek out their forces and to prepare and apply them according to their respective diseases. . . . Permit not the thought to awaken in me: You know enough. . . .[25]

The oaths align the roles of caregiver and researcher. There is no conflict or discord between the roles. The healer and the researcher are at one in their work.

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That healers would also be researchers and develop new knowledge was clear. *How* they would do that, however, was not prescribed. Just as, in 1747, Ship's Surgeon Dr. James Lind could never have envisioned double-blind, randomized clinical trials approved by IRBs, today's clinical researchers may not yet be able to envision a full partnership with empowered patients, capable of contributing more than their physical bodies to the process of research. It is time they do, as patients have earned this right. They have demonstrated their ability to participate in a myriad of ways. It remains for us now, in the research enterprise, to reciprocate by acquiring the skills to work with patients who are prepared to participate with us in mature ways.

To accomplish this, I suggest we now engage in a comprehensive review of our own practices within the public and private sector research enterprise. We should examine every aspect of resource allocation, research design, clinical trial recruitment, and the regulatory interface to determine how we can improve the productivity of research by collaborating with patient groups. This assessment should not be confined to our own soul-searching, but should ask patient groups for their critical review of our historical performance and request constructive comments about how to improve our efforts. On the basis of that review, we should determine what new skills, tools, and research processes we should acquire in order to be better research, regulatory, and policy partners with patients, and we should organize our research ventures accordingly. Next, we should practice these new skills, monitoring the impact on our relationships with patients and on research productivity. Finally, we should recognize that this is a new era of patient participation, that patients' rights to participate, though unrecognized when they first became research subjects long ago, are not new, but merely maturing. It is appropriate that we recognize that now, and mature in our own management of this most critical of relationships in research.

It is not simply by showing that researchers understand these issues that we will rebuild trust, benefit from those patient advocates on the leading edge of leadership, or meet the terms of the oaths we take as healers. Rather, we will do so by proving it through our actions as researchers, regulators, and policy makers.