STRATEGIC HEALTH POLICY INTERNATIONAL

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Global Search for New Knowledge: Covenant in Clinical Trials[1]

New knowledge is the most valuable commodity on earth.
The more truth we have to work with, the richer we become.
—Kurt Vonnegut, Jr., Breakfast of Champions[2]

If the quest for new knowledge brings riches, nowhere is that more true than in health care, where new knowledge brings riches not only for those who seek the knowledge, but also for those who benefit from the resulting research discoveries. Our search for the truth about health and disease and about the causes and cures seems a thirst that cannot be quenched. Each new discovery brings yet another opportunity for new learning and begets new tools and new enthusiasm for pursuing the unknown. The American public is remarkably supportive, with more than 85% saying that the U.S. should maintain its place as a world leader in medical research.[3]

Increasingly, this is not solely a domestic venture for Americans. It is, more and more, a global endeavor. We have sought knowledge in and on foreign soil, to the benefit of all parties involved. Companies have entered into agreements with governments of tropical nations to catalog forest life in search of plant species and soil samples bearing potentially life-saving organisms or properties. Newly identified compounds are being screened against known diseases in hopes of identifying treatments and, better yet, prevention methods or cures.[4]

It is not just the natural resources of the forests that are important to today's research, however. It is people themselves, who form a reservoir of human subjects for research. With greater and greater frequency, investigators are looking to the developing world to identify the subjects who will participate in the development of the new human clinical knowledge that leads to innovative health products. This search is by no means a one-way street. The other nations we visit in search of human subjects are the same nations that seek our help in times of disease crises. We request research subjects to probe the mysteries of health and disease; they request disease detectives from the Epidemic Intelligence Service of the Centers for Disease Control and Prevention (CDC) to probe the mysteries of epidemics. In addition, those nations and ours collaborate in numerous other ventures. We maintain global disease surveillance systems, share medical education assets and participate in global health ventures through the World Health Organization (WHO) and its regional offices. Each of these ventures faces challenges. Some are

under-funded. Others confront language and cultural differences. Still others must perform under adverse weather, geographic, and time zone conditions. The most contentious aspect of this international collaboration, however, concerns the use of human subjects for biomedical research studies.

How did the search for human research subjects turn outside the borders of the U.S. and other developed nations? Is the research conducted according to the same standards as research in the U.S.? Should it be? What is the covenant between the healer, the patient (or, in this case, the research subject), and the community in determining the appropriateness and conduct of the research? How can research studies be done in areas of the world where access to even the most basic clinical care is not the norm? When clinical trials are coordinated across several nations—as they often are—is it unethical to allow local standards and norms of care and of human subject protection to prevail, or should researchers adhere to a single international standard? How is the covenant tested in situations in which the cultural perspectives of the healer/researcher and patient/research subject differ to a great degree and language and ethical standards are widely divergent? Can global clinical trials rely on informed consent as the keystone in the covenant relationship among those involved? Is a covenant possible in global human research? Should we allow standards of research in clinical trials conducted in developing countries to be determined purely by economic considerations? Should we focus on procedures or on outcomes in our attempts to protect research subjects? Is it ethical to pursue biomedical research on subjects in developing countries for diseases common in the developed world? Or should human studies in the developing world be confined to diseases rampant in those countries?

Oaths

Each of the major medical oaths prescribes that healers will seek new knowledge about the workings of the human body and the nature of health and disease. In each, healers invoke all they hold sacred to assist them as they pledge, not only to care for patients, but also to learn more in order to care for them better. It is a sacred duty of the healer. They agree, as part of their obligations to the Divine, their patients, and communities, to study, learn, and share that information with other healers. 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…*[5]

Maimonides was considerably more explicit about research in his prayer:

> *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.*

And also:

> *Grant me contentment in all things, save in the great art. Permit not the thought to awaken in me: You know enough…* [6]

And the Islamic Medical Oath was unmistakably clear:

> *…to strive in the pursuit of knowledge and harnessing it for the benefit but not the harm of mankind.*[7]

That healers would also be researchers and develop new knowledge was therefore clear. *How* healers would do that was less prescribed in the oaths. For certain, the oaths speak generally to ethical conduct in encounters with patients. Patients are to be helped, not hurt. They are to be respected and privacy protected. They are to be granted the best that healers have to offer in terms of time, effort, and skill. Do those same standards of ethical conduct also apply to healers who are not involved in the clinical care of the person, but only in the pursuit of new knowledge as researchers? How should researchers balance the obligations between the quest for knowledge and the care for the human subject, who, in many cases, is a person—a patient—with a disease condition seeking treatment?

Human Clinical Studies

There are many ways to address the requirements of the oaths to develop new knowledge. Epidemiology and other population-based studies yield insights into health and disease states. Not all of these require the time or cooperation of human subjects. Computer simulations and models have certainly contributed to medical knowledge, but even today's sophisticated mathematical models and high technologies are not sufficient to tease all the mysteries from the human body. To fully comprehend the nature of the body and the impact of disease upon it, other methods are required as well. Regardless of the insights from simulations and models, eventually healers must conduct "tests" or "trials," first, using *in vitro*—test tube—techniques; next, with animals; and, finally, on human subjects. Studies conducted in human subjects are called "clinical trials." They are the final phase in the development of drugs and devices that diagnose, prevent, and treat disease. Without these tests, it is impossible to know if the product will be safe and effective for its intended use. Without the costs incurred by the developer and the risks incurred by the patient/research subject, the benefits of the promised therapy will never be clearly known or realized.

While there is no doubt that the techniques of clinical trials existed long before modern medicine, we in the West trace the beginning of clinical trials to the eighteenth century, when six treatments for scurvy were studied in twelve patients.[8] The immediate need of the sailors was not the concern of the investigators; rather, it was the nature of the intervention to prevent scurvy that was important. Although the trial lacked the rigor of modern research, it was the first recorded Western instance of a documented scientific approach comparing the effect and value of a group of interventions in humans.

A modern clinical trial is much more sophisticated than this early instance, but essentially has the same purpose—a *prospective* study to compare the effect and value of an intervention against a control in human beings.[9] This means that an intervention is planned and used selectively in humans to discern whether it will have an impact. When properly planned and conducted, clinical trials are a powerful technique for assessing the effectiveness of an intervention,[10] and they have been called the "most definitive" tool for evaluation of new

products and treatment approaches. They are usually viewed as the research activity with the greatest potential to improve the quality of health care and control costs because they carefully compare alternative treatments.[11] In conducting clinical trials, investigators employ one or more intervention techniques and compare the results to a control group in which no intervention is made.[12] It is from this comparison that conclusions are drawn about the impact and value of the intervention. It sounds simple, but in practice, it is not.

In the earliest days of clinical research in the U.S., human subjects were drawn from pools of patients within this country. Research endeavors were small and initially were funded privately by philanthropists supporting individual researchers. As federal funding grew, starting in the 1950s, the need for research subjects grew as well. These subjects were increasingly drawn from institutions that housed large numbers of accessible research subjects: prisons, schools for the retarded, and the military. By the 1960s, the demand for research subjects grew even more as pharmaceutical companies faced stiff new research requirements under the Food, Drug and Cosmetic Act Amendments of 1962 to demonstrate safety and efficacy of drugs. The skills to conduct these studies also developed and expanded. Paradoxically, over the next twenty years, as the need for clinical research subjects grew, the supply of research subjects gradually declined as local access to new health care technologies improved. This is because prior to the 1980s, many patients sought to participate in studies as a way to access the best medical centers and clinicians in the country. As health care technologies reached local communities, it was no longer necessary to participate in trials to get high quality clinical care. When they could, patients opted to receive care closer to home rather than travel to major medical and research centers where, in addition to receiving care, they would most likely also participate in research.

These factors were already creating competition for human subjects for research in the 1980s, when the nation was stunned by the appearance of HIV/AIDS. As the disease took hold and the search for therapies progressed, the HIV/AIDS community influenced the nature of clinical study participation, creating a research-subject empowerment movement. HIV/AIDS patients became more influential in the conduct of research than any group before them. They participated in the structure of protocols and, as research subjects, even tested their experimental compounds in laboratories to determine if they were getting the active drug or the placebo. Some demanded changes in research design to assure that all patients, at some point in the trial, would have access to the active, hoped-for-therapeutic compound.

A decade later, the research pipelines of federally funded investigators and pharmaceutical developers exploded not only with new HIV/AIDS therapies but with other disease-target products as well, producing an even greater demand for research subjects. In addition, the regulators became more sensitive to the needs of an increasingly diverse American population and sought better balance in gender and ethnic age representation in clinical trials. The National Institutes of Health (NIH) developed web-based communications to attract patients to research trials.[13] Pharmaceutical companies even engaged advertising firms and partnered with practicing clinicians to recruit human subjects. Disease-based patient groups maintained registries of members willing to participate in studies. In the end, none of these efforts succeeded in recruiting a satisfactory supply of human subjects.

By the turn of the century, pharmaceutical companies were anticipating a 65% increase in the number of new compounds coming from their labs, and over 41,000 clinical trials were being conducted by private and public sector researchers. Of clinical trials underway, 80% were not meeting their enrollment deadlines for patients, and 27% of clinical development time was spent enrolling subjects. Industry was incurring losses of up to $1.3 million per day in incomplete trials in the U.S., though it was spending an estimated $1 billion just to recruit patients.[14] Government-funded research was increasingly addressing disease problems of the developing world and pharmaceutical companies were increasingly serving global markets and needed access to patients in those countries that would eventually be markets for their drugs. It should come as no surprise, then, that researchers began in earnest to look abroad for human subjects, particularly in those developing nations that had not already saturated the available clinical trial population with their own research.

It should also come as no surprise that with increased activity came greater scrutiny of the effort. The DHHS Inspector General (IG) studied patient protections in global clinical trials, noting a 16-fold increase in the number of foreign clinical investigations between 1990 and 2000, while the number of countries in which clinical trials were conducted grew from 28 in to 79 during the same period. The IG recommended increased attention to foreign IRB capacity building and monitoring, improved sponsor monitoring, and tracking of studies and leadership from the U.S. to ensure patient protection.[15] An Office of International Activities was created within DHHS to monitor government studies. In the private sector, a new non-profit organization, the Association for the Accreditation of Human research Protection Programs (AAHRP), was formed by a number of medical education and research organizations to develop standards to accredit and guide academic research policies and procedures.[16]

Clinical Care vs. Clinical Research

Whether the research is conducted here or abroad, one of the challenging issues faced by researchers is that clinical *research* is fundamentally different than clinical *care*. Clinical research may occur within clinical care settings, but it has traditionally been viewed as having an entirely separate and distinct purpose. Is it important to distinguish one from the other in order to discuss the ethics that should be present in each?

Clinical *care* is the activity of a healer to improve the patient's well being and attain a desired state of health. Clinical care can take a variety of forms–it can be diagnostic, preventive, convalescent, or supportive. Clinical *research* is the activity of a healer in carefully applying an intervention (as determined in the research protocol) to the patient and monitoring its effects on health or disease. Even though the clinical care provided to individuals involved in clinical research may be the same as provided in clinical care absent research, the respective purpose is different. Should the roles and expectations of the parties then be different as well? Clinical care is guided by a set of clearly-defined medical ethics. Can and should those ethics now be applied to clinical research, even though care of the patient is not the ultimate goal? What are the appropriate ways to ethically conduct research abroad, particularly in countries where the language, notions of disease, economies, and culture are radically different from those in the U.S.? These questions are challenging, and they are made all the more so by a history in which

the ethics of clinical care were not applied to clinical research. As these lapses were often to the detriment of the research subjects/patients, this history has eroded confidence in the ethics of the research enterprise, making the consideration of global clinical trials dangerous waters for the unwary.

Ethical Lapses in Clinical Research

There are notable examples of dangerous and harmful experiments performed on non-consenting patients. In the most egregious cases, nonconsensual experiments have been performed on captive people in institutions, particularly those regarded as "lesser humans," such as Jews in Nazi concentration camps, the mentally retarded in institutions, persons of African descent, and indigent patients. Most often, these were people who were unable to decline or reject their participation in the research study.[17] In some cases, informed consent was not sought or obtained, although the consequences for the patient were potentially harmful. In some cases the researcher, often a physician, fraudulently described an experimental procedure as either a diagnostic procedure or a treatment for the patient's condition, including cases where there was no reason to believe that the patient might benefit from the experiment.

Our modern perspective on research ethics came about largely because of these revelations, particularly those regarding the medical experiments conducted by doctors in Nazi concentration camps. However, abuse of human subjects was not confined to the Nazi regime, nor were abuses confined to prisoners. In 1963 American researchers injected live cancer cells into elderly debilitated patients in a Jewish chronic disease hospital.[18] In another incident, intellectually disabled children were injected with hepatitis in a New York State public institution.[19]

One of the most widely known incidents of its type, the Tuskegee syphilis study, came to light in the 1970s. From 1932 until 1972, nearly 400 African-American men from the rural south diagnosed with 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. The study was no secret among physicians who worked on sexually-transmitted diseases, and results from this experiment were published in medical journals for over thirty years. It was not until 1965, nearly twenty years after penicillin was demonstrated to be effective against syphilis, that clinicians objected to the experiment on ethical grounds. It was 1972 before a reporter from the Associated Press (AP) was tipped off, broke the story, and brought the study to attention of the public.[20]

It is no surprise that the Tuskegee study continues to affect attitudes about clinical research within the African-American community, 81% of whom are familiar with its history (as compared to only 28% of whites). As a result, just over half of African-Americans who know about the study are now reluctant to participate in clinical trials, versus only seventeen percent of whites.[21] It is astonishing that mainstream American medicine was so blind to the ethical issues involved in withholding care–especially after penicillin was discovered to be an effective treatment–and that these studies could be allowed to continue for such an extended time. The medical research community clearly failed in its ethical responsibility to these men, and others

who were research subjects without their knowledge and consent.[22]

The Tuskegee study was, unfortunately, consistent with other studies and was typical of practices in clinical research prior to our relatively recent concern for human subjects. In the Tuskegee study the issue was informed consent.[23] In other studies, prisoners were subjected to malaria, typhoid, and cholera. Given that most reasonable healthy persons would be unlikely to subject themselves to such risks, ethicists have since questioned the extent to which their consent was voluntary and recently have wondered if prisoners, given their dependent circumstances, can give their consent at all.[24]

In another study, the issue was compassion: a famous gynecologic surgeon conducted surgical experiments on African-American women without anaesthesia, because he believed that they did not suffer and would "bear pain" better than white women.[25] These practices, unethical by today's standards, were by no means only an American phenomenon, nor were they solely historical. A high-profile report questioning international clinical trials raised concerns and attracted the attention of Congress in the year 2000.[26] In New Zealand, a hospital ethics committee and Institutional Review Board (IRB) approved a study that denied treatment to women suffering from cervical cancer. The women were not told of their diagnosis or of the research study, though they were repeatedly brought back to the hospital for observation. Many died when timely treatment could have saved their lives.[27]

By the time the U.S. National Commission for the Protection of Human Subjects on Biomedical and Behavioral Research issued its report in 1979, it was clear that the risks, burdens, and benefits of research were out of balance. The risks and burdens of research subjects were falling largely upon the poor and the disadvantaged, while the benefits of improved medical care were being granted primarily to the more advantaged of society.[28] Might that be true today as we seek to conduct clinical trials overseas? How do we, in this nation, respond in ways that support the development of new knowledge while accommodating the complexities of global clinical trials?

Setting Ethical Standards

The global community responded to the research conducted by Nazi doctors, calling them crimes and crafting the Nuremberg Code. The Code constituted the first international normative framework to regulate standards in clinical research trials.[29] This document was subsequently superseded by the Declaration of Helsinki, which became a code for research and experimentation endorsed by the World Medical Association (WMA) in 1964. The Declaration of Helsinki has since been revised on five occasions to keep pace with the progress of science and ethics,[30] and it is one of at least a dozen national and international standards directing ethics in research. What medical oaths lack in specificity, the scientific, regulatory and clinical communities now provide.[31]

Informed Consent as the Keystone of Ethical Research

For many years, the informed consent of the research subject was the key factor in assessing the ethics of the study. Institutional Review Boards (IRBs) were created to assure that

investigators take research subjects' interests into consideration, particularly those related to consent. Authoritative guidelines for research defined informed consent as a *process* by which an individual voluntarily expresses his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to his or her decision to participate.[32]

The mechanics of informed consent for human research protocols have been carefully defined and detailed by institutional, governmental, and global organization regulations. Because these standards emphasize the *process* of obtaining consent and not the *documents* produced, securing valid informed consent is a complex process that involves multiple, interrelated elements. Valid consent comes only when the research subject has the capacity to understand and decide whether or not to participate and authorizes that decision voluntarily. That decision can be made only when all of the necessary information is disclosed.[33] In the U.S., while the burden of ensuring informed consent lies with the physician, the ethical standard recognizes informed consent as shared decision making that involves the patient, physician, nurse, family, and all those with an ethical interest in the patient.[34]

In an ethically sound consent process, a member of the research team provides information to the potential subject and determines that the subject understands the information. The subject then must voluntarily agree to participate. In the documentation of the process of informed consent it is essential that the subject signs or otherwise indicates his or her agreement to participate. Many settings also require that the investigator who obtains the consent signs the consent form or other related documents and a witness (or person designated by the participant) attests to the process. The disclosure requirements in the U.S. are codified in the Federal Policy for the Protection of Human Subjects at 45 CFR 46.116(a).[35] The "basic elements of informed consent" set forth in these requirements for clinical trials include:

> (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
>
> (2) A description of any reasonably foreseeable risks or discomforts;
>
> (3) A description of any benefits to the subject or to others, which may reasonably be expected from the research;
>
> (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject;
>
> (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
>
> (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of; or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Challenges to Informed Consent in Global Clinical Trials

American investigators are bound by American ethics requirements if the data from a study are to be used in the approval of therapies regulated by the FDA for the U.S. market. Although those standards allow for modifications based on local circumstances in developing countries, there is little guidance concerning how adaptations should be made. This makes the informed consent process as potentially uncertain from a regulatory perspective in the U.S. as it can be daunting from other perspectives in the foreign land.

Some of the challenges are economic, with some of these nations lacking the basics in even housing, food, transportation, and energy. It is no wonder, then, that the public health and clinical care infrastructures in these countries are also fragile. There are few systems for collecting data on the health of the population or the prevalence of diseases in the nation. Facilities are not readily available for identifying and screening study participants. Clinics lack basic medical supplies and are understaffed, even when the most basic conditions are being treated or researched. Despite such barriers, however, ethical clinical research can be conducted. Even many of the poorest countries have an educated class of clinicians, ethics committees, scientific peer reviews of research protocols, and local scientists and governments that are qualified to determine if the research may ultimately benefit the country.[36]

Some of the challenges are cultural. In some countries, for example, individual consent on many matters important to life is not a commonly held value; hence, the notion of individual consent in research must be imposed upon the citizens by the government and the participating research teams. In those nations, 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.[37] The age of majority also varies around the world. In the U.S., the legal age for consent is 18, but in many other countries it is much younger.

Some of the 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 in the research. This can be problematic in countries with low rates of literacy[38] or in countries where citizens fear that signing a document may place them or their families at risk of reprisals from an oppressive government.[39] Informed consent is also problematic in countries where the language has no words for "research study."[40] Host country representatives can translate consent forms, but agreeing on a form that is both culturally

acceptable in the host nation and consistent with U.S. regulatory agencies is no small undertaking.[41] 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.[42, 43] Some regulatory requirements common in the U.S. cannot be adopted overseas. Requiring the name and telephone number of a research contact and a human rights contact, for example, is impossible in a country where people do not have telephones.

Increasingly, the challenges are political as well. Even in the developed world, researchers encounter subjects who enter the trial in order to receive health care, not to be part of developing new knowledge. Patients, trusting in their physicians in clinical settings, believe that the investigators are acting as their physicians—in other words, as *clinician* healers, rather than as *researcher* healers.[44] This phenomenon, known as "therapeutic misconception," is widespread throughout the world. It is at the cutting—and bleeding—edge of research ethics today.[45] Therapeutic misconception rests on the confusion between the aims of research and the aims of medical treatment of patients. It is by no means a developing-world phenomenon, though it is likely to be more prevalent in developing countries for several reasons. First, patients may rarely receive care at all or may receive care only in government-controlled settings in which other forms of consent and individual choice are not the norm. The trust, dependency, and power in the patient-physician relationship transfer to the research encounter. Second, international advocates, acting as surrogates to promote the interests of the research subjects, often intervene to ensure that care is provided in the context of the research study.

Informed Consent Not the Sole Ethical Touchstone

Current federal regulations in the United States require IRBs to determine that "risks to subjects are minimized by using procedures which are consistent with sound research design."[46] The regulations further require that "risks 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."[47] While the federal regulations do not tell IRBs to review the scientific merit of a research design, research with flawed methodology will not generate valid or reliable data about the efficacy of the experimental intervention. In such cases, participants will incur the risks, inconveniences or discomforts of being involved in research that lacks the potential to produce general and beneficial knowledge. Thus, the scientific merit of research is an ethical issue because it would be unethical to put people at risk or even to inconvenience or discomfort them through participation in a poorly designed study. IRBs, therefore, assess both the scientific and the ethical aspects of the protocols they review.[48]

At long last, these considerations—which go beyond those of informed consent—are being addressed by ethicists now working to detail additional ethical requirements for clinical research.[49] Their continued exploration of these issues greatly enriches the notions of covenant that should be embedded in the pursuit of new knowledge using human subjects today, in all places on the globe. These new elements suggest that the study should have social or scientific value and should be conducted in scientifically valid ways because scarce resources (financial or human) should not be spent on projects that are unlikely to benefit mankind. They suggest that

justice requires that subjects be selected in ways that are fair and do not stigmatize, or make vulnerable, someone who may be a participant. They propose that the poor and powerless should not be chosen for more risky (or less beneficial) research, while the rich and powerful are chosen for less risky (or more beneficial) studies. They also suggest that there be independent reviews of the research in order to assure public accountability and minimize potential conflicts of interest. Finally, in addition to informed consent, they believe that respect for human subjects should be demonstrated by allowing them to withdraw from the study, by protecting their privacy, by informing them of study results—including both risks and benefits—and by maintaining their welfare during the trial.

This last issue is at the cutting edge of ethical considerations in global clinical trials. In 1991 and 1993, the Declaration of Helsinki was supplemented by international research ethics guidelines produced by the CIOMS in collaboration with the (WHO. This set of documents proposes new protections from exploitation for participants in research, and a critical new benefit as well. In this iteration of the global standard of ethics, sponsoring agencies are called upon to ensure that, at the completion of successful testing, any product developed can be made reasonably available to those in the developing nations in which the research was conducted.[50]

The importance of this proposal, as well as the minefield of ethical issues, became apparent in a recent controversy regarding global clinical trials. A North American company prepared to study a surfactant product in premature infants with idiopathic respiratory distress syndrome (IRDS).[51] Since a product for this condition was already approved in the U.S., testing against a placebo—no therapy—in the U.S. would have been an ethical breach. Likewise in the U.S., it would have been unethical to select infants for an experimental—unknown—therapy when a known therapy was available. As a result, the company turned to Latin American countries where products were not available in some locations, proposing to do the research there. The company and its advisors reasoned that infants receiving the experimental product would actually receive a higher standard of care than what was otherwise available. Significant objections from critic groups were raised with the Food and Drug Administration (FDA) on the grounds that infants in Latin America deserved the same standard of care as those in the U.S., making the research company a party to the delivery of care. In its response, the company exposed its design committee makeup, ethics advice, clinical trial plans, and subsequent marketing and medical education plans. Beyond that, this example demonstrated the degree to which conducting research in the developing world is not only a matter of good clinical and ethical design, but a matter of equitable access to care on a global scale, enforced through public pressure and politics, to ensure current and future clinical care.

Maturing Covenant in Global Research Ventures

There is little doubt that the advances in medicine since the early seventeenth century when modern biomedical research began have greatly extended average life span, reduced morbidity and improved the quality of life in both the developed and developing worlds. There is little doubt that health care will continue to require human subject research in order to continue to make progress in addressing both the prevalent and emerging diseases of the world. We owe a great debt to the scientists and clinicians that created innovative and dynamic experiments for the

advancement of medical technology and science.

However, any progress made in developing new knowledge depends on the willingness of those individuals who participate in studies as research subjects and who risk pain, disability, and even death as they face the unknowns. We owe a great debt to them as well. It seems clear that most people will acknowledge that a covenant exists between those who conduct clinical research—the healers—and those who participate in it—the patients. It is time, now, to include in that covenant those who benefit from research—the community. The time has come to construct a covenant that can address the complexities of a research enterprise that is no longer confined to one nation, but that covers the globe in an attempt to better address all the diseases of the world. This covenant would find ways to deal with the complications of this global scale, where the communities within which research is conducted and the communities where the researchers are based have many cultural, socioeconomic, and political differences.

The challenge for U.S.-based researchers lies in satisfying many masters. One of those masters is the imperative for sound clinical trial design. Another is the need for adherence to sound ethical principles in research that have been described here. Another is adherence to U.S. regulation. Yet another is sensitivity to local and global cultural differences.

The major driving force in the U.S. is regulation. In essence, the United States bundles its research regulations, its ethical principles and the commitments that underlie them as part of the research projects it exports. Consequently, collaborative research protocols conducted abroad need approval not only of officials of the host country and local research institution, but also of the IRB at the investigators' or sponsors' home institutions. Protocols also need the approval of the FDA that will rule, ultimately, on whether the research can be used for product approvals. Yet existing rules and regulations governing the conduct of U.S. investigators (and others subject to U.S. regulations) may impede international collaboration and unnecessarily complicate or frustrate research projects. Just as ethics is not a trivial matter, neither is the delay in important research. How do we find a balance between the need for new knowledge and the imperative to treat human subjects in the most ethical ways? How do we balance the hunger for new therapies in a wealthy nation like ours with the contributions that the poor of the world make to our health as they agree to participate in studies that develop products they may not be able to afford? Where do the responsibilities of the healer/researchers end, and those of the American community begin?

It is difficult to reach the answers to those questions from purely research, economic, or bioethical discussions. These questions call for the participation of more parties—parties to the covenant of research. Complexities abound, yet there is little doubt that despite complex realities, ethical precepts, and multinational interests the end result will still focus on the relationship between individual healer and patient—even if in this case they are called researcher and subject.

- The patient has two faces—the one participating in the trial and the one whose fate that trial could ultimately affect. Both are important. For that reason, perhaps it is no longer ethical to speak of "therapeutic misconception." Perhaps the time has come for all *research* to also *care*, not just for the patient who will receive the research-

demonstrated therapy from pharmacy shelves, but also for the one who agrees to place his or her own life, health, and comfort on the line to get the proof. The research covenant exists first within its own microcosm, where only the relationship between healer and patient exists; where the abilities of the healer nurturing the patient, and the reciprocating trust and compliance of the patient, should be the sole litmus test of what is, and is not, appropriate.

- The researcher has two faces as well. He or she is both healer and investigator, caregiver to a patient and objective monitor of a research protocol. Particularly in the global research arena, wearing both faces across cultures that may differ greatly from one's own will require guidance from the local community. Principles, dictums, and ethical guidelines are all helpful, but there will never be a substitute for making the global, local.

- It is for this reason that the dialogue with local communities, however they are defined in other nations, must be frequent and careful. In many global studies, the diagnostic, educational, and therapeutic interventions exceed the standard health care practices of the host nation, but are still inferior to those offered in the U.S. Only the local community can determine whether this is tolerable. Research subjects and their national regulators and researchers should be given the opportunity, if they so choose, to participate in trials that are incremental steps toward better care in their nation. The perfect, in some nations, might well be the enemy of the good. Decisions about when this is the case can be made only by the people and the nations involved.

- When the studies are feasible in the host country in terms of cost, public health infrastructure and cultural norms, but inferior to those of the U.S., are they unethical? Though federal regulations clearly state that a country's cultural standards and norms should be taken into account, little guidance is provided concerning how to do that.[52] Efforts to do so should begin. The American public, if it desires an acceptable ethical standard that matches what it would anticipate in this country, should also be prepared to provide the funding, through public resources or product purchases, to ensure that the necessary resources are available when the trials are undertaken.

- Oversight of international clinical research should apply to all research, regardless of source of funding and purpose. Further, oversight should entail consultation, education, and consensus-building about the value and methods of the research project and not just regulatory restrictions and delay-causing requirements.

- Americans, too often unwilling to participate in clinical trials themselves, should increase their participation in research as subjects. Today's plentiful treatment options are the result of the participation of past generations in research. We, who now benefit so greatly, now owe it to future generations to join forces with researchers today in the search for new knowledge.

The world today faces a large number of unresolved health and disease concerns and a

rapidly emerging set of new research methods. The needs of the poor in the developing world for health care will continue to run headlong into the American frontiers of biomedical science. This should sound a call for a dialogue among those who design, conduct, and participate in the quest for new knowledge, and, increasingly, this dialogue should involve the rest of us who will benefit from their efforts. It is a positive sign, indeed, that concern for research subjects in other nations has emerged as a public policy issue in the U.S. It is, in some small way, an indication of our rightful stewardship over U.S.-based research ethics. Now is the time, however, to consider the consequences and to own up to the complexities and costs as we move forward to do adhere to the standards we promote and hold dear.

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[1] This appeared originally in 2001 in *Covenants: Inspiring the Soul of Healing*. Readers interested in exploring covenants in greater depth can find background in *The Origins of Healing as Divine Gift* and *History and Modern Applications of Covenant Healing Traditions* which appear in this series.

In summary, healing traditions are based on ancient views that healing skill came from the divine. Healers were aligned with divine forces against the terrible, unknowable and sometimes evil forces of illness. As a result, healer-patient relationships were structured as covenants. Covenants differ from contracts. Contracts have a defined beginning and end and specify the duties of the parties in detail. Covenants do not end and do not detail the duties of the parties.

There are two types of covenants, both are relevant in health care and are expressed in oaths taken by clinicians and others in health care. The first type – a covenant of *grant* – defines what one party does for another, without conditions or expectations. Parents have covenants of this type with their children, providing them food, shelter, clothing and protection. The second type – a covenant *of obligation* – involves mutual promises between the parties. Spouses enter into this type of covenant '…for better or for worse.'

The *Oath of Hippocrates*, a classic covenant statement, contains both types. It creates a covenant of *obligation* with other healers, calling for the oath-taker to "…study, learn and teach my fellows…and to treat his sons as my sons." Then, the oath "…grants health…" to the patient. The *Prayer of Maimonides*, an oath created later, contains the same covenant of *obligation* among healers and calls patients into a covenant of *obligation* as well, asking that patients follow medical advice, take prescriptions and avoid the advice of meddlesome friends and relatives uninformed about health and disease.

The book suggests that everyone in health care – not just clinical experts but those in any role in research, management, insurance, health reporting and even policy – are the sophisticated extension of ancient tribal healers. Our societies are more complex, as is our knowledge, our data and information, our technology and our systems of providing care. As a result, as healers we have entered healing streams of an ancient origin. Our patients and communities expect us to ascribe to these covenant values.

In my view – and I am not alone in this – health required the integral relationship among healers, patients and communities. I therefore proposed three steps to transform health: first, a covenant of obligation among all healers, as I broadly defined them; second, a covenant of obligation with patients; and third, a covenant of obligation with communities, as well.

This is an application of those ideas to the policy issues addressed here.

[2] Kurt Vonnegut, Jr., *Breakfast of Champions* (New York: Dell Publishing, 1973) p. XX.

[3] Poll Data Booklet, Vol. 2, Research!America, p. 2. Also available at http://www.researchamerica.org/opinions/2000polls.generalversion_files/frame.htm. Accessed January 7, 2002.

[4] Merck & Co., Inc. established a relationship with the Instituto Nacional de Biodiversidad of Costa Rica to support the search for and cataloging of plants native to that nation's rain forests, in return for the rights to screen those

products for bioactive compounds. Available at http://www.inbio.ac.cr/en/inbio/Inbio.htm. Accessed November 21, 2001. Shaman Pharmaceuticals is a company devoted to producing medicines from natural sources in the rain forests. Additional information can be found at: http://www.well.com/user/hlr/tomorrow/shaman.html. See also http://www.shamanbotanicals.com. Accessed November 21, 2001.

[5] Charles G. Cumston, *An Introduction to the History of Medicine* (London: Dawson's of Pall Mall, 1968) p. 86.

[6] Irving I. Edgar, *The Origins of the Healing Art: A Psycho-Evolutionary Approach to the History of Medicine* (New York: Philosophical Library, 1078) p. 137.

[7] "Islamic Code of Medical Ethics, Declaration of Kuwait," adopted by the International Conference on Islamic Medicine, 1981. Available at http://www.phrusa.org/research/medicsoath.htm. Accessed October 31, 1999.

[8] J.P. Bull, "The historical development of clinical therapeutic trials," *Journal Chronic Disease* (1959) 10:218-248.

[9] L.M. Friedman, C.D. Furberg, and D.L. DeMets, *Fundamentals of Clinical Trials*, 3rd ed. (New York: Springer Publishing, 1998).

[10] F.L. Iber, W.A. Riley, and P.J. Murray, *Conducting Clinical Trials* (New York: Plenum, 1987).

[11] NIH inventory of clinical trials: Fiscal Year 1979, Vol. I. National Institutes of Health, Division of Research Grants, Research Analysis and Evaluation Branch, Bethesda, MD.

[12] Friedman, et al., *Fundamentals of Clinical Trials*.

[13] The archive of NIH Clinical trials can be searched at http://clinicaltrials.gov. Accessed November 21, 2001.

[14] Kathleen Drennan, "Have the ultimate benefits of clinical trials been maligned beyond repair?," *Drug Discovery Today* 6 (12): 597-599.

[15] *The Globalization of Clinical Trials: A growing Challenge in Protecting Human Subjects,* Department of Health and Human Services, Office of the Inspector General, December 2001, OEI-01-00-00190. Available at http://oig.hhs.gove/oei. Accessed January 13, 2002.

[16] The group of founding members includes Public Responsibility in Medicine and Research, the Association of American Universities, the Association of American Medical Colleges, the National Health Council, the Consortium of Social Science Association, the Federation of American Societies for Experimental Biology and the National Association of State University and Land-Grant Colleges. Representatives of the public will join the board of the group and institutions will apply for accreditation, which can be granted following site-visits to the institution and adherence to guidelines and principles of the group.

[17] R.B. Standler, "Nonconsensual Medical Experiments on Human Beings," May 1999. Available at http://www.rbs2.com.

[18] Katz, *Experimentation with Human Beings*, 1972, pp. 9-65.

[19] The Willowbrook Hepatitis study was carried out from 1963 to 1966 at the Willowbrook State School, an institution for "mentally defective persons." Some children were deliberately injected with the hepatitis virus, others were fed extracts of stools from infected individuals, and still others received injections of purified virus. Information is available at http://hstraining.orda.ucsb.edu/training/willowbrook.htm. Accessed July 5, 2001.

[20] James H. Jones, *Bad Blood: The Tuskegee Syphilis Experiment* (New York: Free Press, 1993).

[21] Vickie L. Shavers, Charles F. Lynch, and Leon F. Burmeister, "Knowledge of the Tuskegee Study and its impact on the willingness to participate in medical research studies," *Journal of the National Medical Association*, December 2000, 92 (12), pp. 563-572.

[22] A article by Henry Beecher reviews 22 studies, conducted in prestigious medical institutions and published in prestigious journals, where human subjects encountered risks without their knowledge or consent. Henry Beecher, "Ethics and clinical research," *New England Journal of Medicine (NEJM)*, 274 (1966): 1354-60.

[23] P.M. McNeill, "Experimentation in human beings," In H. Kuhse and P. Singer (eds.) *Companion to Bioethics*, (Oxford: Blackwell, 1998) pp. 369-378.

[24] G.J. Annas, L.H. Glantz, and B.F. Katz, *Informed Consent to Human Experimentation* (Cambridge, MA: Ballinger, 1977).

[25] Cited in Martin S. Pernick, *A Calculus of Suffering: Pain, Professionalism and Anesthesia in Nineteenth-Century America* (New York: Columbia University Press, 1985) p. 156.

[26] Joe Stephens, "The Body Hunters," *The Washington Post*, December 17, 2000, A01. This was the first of a six-part story that appeared between December 17 and December 22, 2000. The series is available at htsp://washingtonpost.com/wp-dyn/world/issues/bodyhunters/. Accessed December 22, 1000

[27] P.M. McNeill, *The Ethics and Politics of Human Experimentation* (Oakley: Cambridge University Press, 1993).

[28] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* U.S. Government Printing Office, Washington, D.C, 1979.

[29] *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10: Nuremberg, October 1946-1949,* 2 vols. U.S. Government Printing Office, Washington, D.C.

[30]"World Medical Association Declaration of Helsinki, "Ethical Principles for Medical research Involved in Human Subjects," *Journal of the American Medical Association (JAMA)*, December 20, 2000, Vol. 284 (23), pp 3043-3045. For other U.S.-focused principles, see especially the work of the National Bioethics Advisory Commission, including reports on *Ethical and Policy Issues in research Involving Human Participants*, and *Ethical and Policy Issues in International Research Clinical Trials in Developing Countries*, available at http://www.georgetown.edu/nbac. Accessed December 17, 2000.

[31] Ezekiel J. Emanuel, Dadid Wendler, and Christine Grady, "What Makes Clinical Research Ethical?," *JAMA*, May 24/31, 2000, Vol. 283 (2), pp. 2701-2711.

[32] International Conference on Harmonization, *Harmonized Tripartite Guideline* and *Guideline for Good Clinical Practice* (1996). Information available at http://www.ifpma.org.

[33] T.L. Beauchamp and J.F. Childress, *Principles of Biomedical Ethics* (New York: Oxford University Press, 1986) pp. 30-34, 133-38.

[34] R.J. Boyle, *The Process of Informed Consent. Introduction to Clinical Ethics*, 2nd ed. (University Publishing Group, 1997) pp. 91-93.

[35] *Federal Policy for the Protection of Human Subjects*, 45 CFR 46.116(a) 1-8.

[36]Marjorie A. Speers, Ph.D., *Basic Protections for Human Subjects in International Research*, Centers for Disease Control and Prevention (CDC).

[37] Ibid.

[38] Ibid.

[39] Multiple sources, but primary discussions on subjects contained in Council for International Organizations of Medical Sciences (CIMOS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, WHO, Geneva, 1993.

[40]Speers, *op. cit.*

[41] Ibid.

[42] CIOMS,*op. cit.*

[43] N. Dickert and C. Grady, "What's the Price of a Research Subject? Approaches to Payment for Research

Participation," *NEJM* 341(3) (1999): 198-203.

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[45] P.S. Appelbaum, L.H. Roth, and C.W. Lidz, "The Therapeutic Misconception: Informed Consent in Psychiatric Research," *International Journal of Law and Psychiatry* 4(3-4) (1982): 319-329.

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[47] Ibid.

[48] N. Kass and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations" (2000). Information available at http://www.NBAC.org.

[49] Emanuel, Wendler, and Grady, *op. cit.*

[50] CIOMS *op. cit.*

[51] Public Citizen's appeal to the Secretary, U.S. Department of Health and Human Services (Health Research Group Publication #1558) can be accessed at www.citizen.org/publications/release.cfm? ID=6761. Accessed January 7, 2002. Discovery Laboratories, Inc. response and research plans can be found at www.discoverylabs.com. Accessed January 7, 2002.

[52] P.S. Applebaum, L.H. Roth, and C.W. Lidz, "The Therapeutic Misconception: Informed Consent in Psychiatric Research," *International Journal of Law and Psychiatry* 5(3-4) (1982): 412-419.