A World of Research Subjects: Informed Consent and Benefit Sharing*

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The most important question for any research project is whether the research should be done at all. Only after this is answered do issues of how and where to do the research become relevant. When doing research in another country, however, the whether and where questions become intertwined. This is because the recent globalization of clinical trials is itself suspect. What is the motivation for the sudden upsurge in clinical trials in other countries? Who benefits from the globalization of research, and who is put at risk? Some advantages have been suggested, including reduced regulation, less oversight, decreased costs, and more rapid results, but none of these alone (or together) is sufficient to justify the expansion of medical research to an underserved, disenfranchised, and exploitable population. The only justification is that the proposed research addresses a question that can only be answered by this unique population and the results must bring short- and long-term benefit. The research remains suspect until ethical norms are met. The subjects must never be worse off from participating in the trials than if they had never participated.

In international clinical research the focus must be on a health problem in the host country. There is a need to both gather facts and to make value judgments. The most important fact is whether or not there are disease conditions unique to the population that cannot be studied in developed countries or in the sponsor's home country. The other critical fact is what diagnostic and therapeutic modalities exist locally prior to the proposed study. Value issues include: what ancillary medical support should be provided as part of the design of the study? What is the justification for use of a control arm and what should be provided to control participants? What health care must be provided to all participants even if it is not necessary for design of the study? At the conclusion of the study should every subject be assured access to prophylactic diagnostic and therapeutic methods found effective? As a result of the study, if there is an effective product that cannot be provided to the general population of the host country, then the trial is not justifiable. The clinical trials of pulmonary hypertension in the developing world raise serious questions at all levels of ethical justification.

The globalization of clinical research would seem to call for more effective ethical and legal rules to protect both research subjects and scientific integrity.[1] Some observers noted more than a decade ago that research was being conducted in developing countries without concern for adherence to the international ethical principles for human-subjects research contained in the 1947 Nuremberg Code and the 1964 Declaration of Helsinki.[2] Confusion continues in many quarters. For example, the Food and Drug Administration (FDA) decided that research studies submitted for review need not be bound by the Declaration of Helsinki—they must only follow the industry-sponsored Guidelines for Good Clinical Practice outlined by the International Conference on Harmonisation.[3] The decision on the Declaration of Helsinki was reasonable—as that is a code developed by physicians for physicians, and is the only declaration that makes consent optional with the physician in the case of "therapeutic research." The Guidelines for Good Clinical Practice, on the other hand, are industry-sponsored guidelines that are meant to make research more efficient rather than more ethical. The "harmonization" process is an industrial one that seeks to regularize and homogenize that which is unique to specific protocols, places, and research subjects. The challenge of conducting ethical research around the world is real; the solution has been elusive.

We focus on 2 aspects of ethics research that have been the most contentious in the past, but about which we believe there is now ethical consensus: informed consent and benefit sharing. We will use 2 examples to explore and explain the current ethical consensus: one the subject of major litigation in the US (on informed consent), and the other (on benefits) the subject of continuing commentary in the medical ethics literature. It should be emphasized at the outset that there are no special research rules for specific conditions or diseases, and thus no special ethics rules for research on pulmonary hypertension. [See Box 1.] The rules, as they exist, apply to all research. There may, however, be practical application questions—such as how to document informed consent, and how to ensure that research subjects are not exploited, that may vary based on disease, geography, population, socioeconomic and educational status, and the availability of health care.

INFORMED CONSENT

The doctrine of informed consent has been the centerpiece of ethical research on human subjects at least since World War II. It was best articulated by US judges sitting in judgment of the Nazi physicians at Nuremberg in 1947, in what has be-

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Box 1: ETHICAL CONSIDERATIONS
Important study, appropriate subject and time
Good scientific design to answer question
Minimize risk to subject
Competent investigators and adequate facilities
Favorable balance of risks and benefits
Voluntary informed understanding consent
Rights of subject to decline and withdraw
Just distribution of risks and benefits
Equitable selection of subjects
Special justification for use of vulnerable population
Monitoring of data to ensure subject safety
Protection of privacy of subjects and maintenance of confidentiality
Compensation for research-induced injury
Follow-up on health of subject

come known as the Nuremberg Code. [See Box 2.] The first item of this 10-point code could not be clearer in its requirement: "The voluntary consent of the human subject is absolutely essential . . . [and includes] legal capacity . . . free power of choice . . . sufficient knowledge and comprehension of the [nature, duration, and purpose of the experiment] . . . to make an understanding and enlightened decision." The consent requirement was later incorporated into international human rights law in the International Covenant on Civil and Political Rights, a treaty that was open for signature in 1966, and became effective in 1976: "No one shall be subjected to torture or to cruel, inhuman, or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation."

Medical groups, at least some of which were not entirely pleased to have judges and governments making binding decisions about medical research, developed the Declaration of Helsinki under the auspices of the World Medical Association. First promulgated in 1964, this declaration has since been revised 8 times. Its basic rule on informed consent reads: "The physician should obtain the subject's freely-given informed consent, preferably in writing. . . . [But in clinical research] if the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to [an] independent committee." International Ethical Guidelines for Biomedical Research Involving Human Subjects (published in 1993, and since

Box 2: THE NUREMBERG CODE [From International Military Tribunal. Trials of war criminals before the Nuremberg Military Tribunals under Control Council Law no. 10. Washington, DC: Government Printing Office, 1950. Military Tribunal Case 1, *United States vs. Karl Brandt et al*, Oct 1946 to Aug 1947]
1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him/her to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is a prior reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

revised by the Council for International Organizations of Medical Science) state: "The investigator must obtain the voluntary, informed consent of the prospective subject [or legally authorized representative]. . . . Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee." Given these different and differing codes of research ethics, it seems reasonable to clarify their status. Most specifically, what is the status of the Nuremberg Code, which was set forth by judges in an international trial and was based on what they believed to be international law? Since 9/11 the US has seemed to treat international law with a degree of contempt, at least when compliance with such law was seen to compromise national security or to stand in the way of "enhanced interrogation" (ie, torture) to obtain information thought necessary to prevent another terrorist attack.

The recent informed consent litigation involves what has become a notorious case of human experimentation on children conducted by US researchers in Kano, Nigeria, during a meningitis epidemic in 1996. The story was reported by the *Washington Post* in 2000 and created a sensation.[4] It described the slow death of a 10-year-old girl known only as Subject 6587-0069. The researchers, who were working for Pfizer, monitored her dying without modifying the experiment, following the protocol designed to test their antibiotic Trovan (trovafloxacin) in children, against standard medical care for meningitis. The *Post* noted that its investigation had uncovered other such corporation-sponsored experiments "in Africa, Asia, Eastern Europe, and Latin America" that were "poorly regulated" and "dominated by private interests"—studies, it remarked, that "far too often betray" their promises to research subjects and consumers.

After the exposé was published, the families of the Kano child-subjects brought suit against Pfizer in Nigeria and later in the United States, charging the company with failure to obtain informed consent to experimentation. Pfizer had initially and successfully argued in court both that there was no international norm requiring its physicians to obtain informed consent for the use of experimental drugs, and that any lawsuit against them by subjects and their families should be tried in Nigerian, not US, courts. Pfizer abandoned this latter claim when, in 2006, an internal report on the experiment by the Nigerian Ministry of Health was made public. The report concluded that the study violated Nigerian law, the Declaration of Helsinki, and the United Nations' Convention on the Rights of the Child. The Nigerian government then filed both a criminal and a civil suit against Pfizer in Nigeria. A settlement in this case has since been reported, although there continue to be conflicting reports about whether the families have or will accept the amount of monetary compensation offered (reportedly $70 million).

More important than the case in Nigeria, however, is a case concerning the same experiment, which has been ongoing in the US for almost a decade. The latest decision from the US Court of Appeals for the Second Circuit, which covers New York, Connecticut, and Vermont, handed down in January 2009, reversed a trial court's dismissal of the US lawsuit against Pfizer and sent it back for trial.[5] The case has not yet been tried (and may, like the Nigerian case, ultimately be settled out of court), and if it is tried, the Nigerian families may not be able to prove the facts they have alleged. Nonetheless, for the purposes of deciding whether the families could have their day in a US court, the Second Circuit had to assume that the allegations are true. These allegations are primarily that in the midst of a meningitis epidemic in Nigeria, Pfizer dispatched physicians to the Kano Infectious Diseases Hospital to conduct a study involving 200 sick children, comparing the efficacy of oral Trovan with the FDA-approved antibiotic ceftriaxone (Rocephin). Trovan had never been tested in children in its oral form. The phase 3 trial, in which half the children were given Trovan and the other half received a low dose of Rocephin, was conducted over a 2-week period, and then the Pfizer team abruptly left. According to the families, "the tests caused the deaths of 11 children, 5 of whom had taken Trovan and 6 of whom had taken the lowered dose of ceftriaxone, and left many others blind, deaf, paralyzed, or brain-damaged." The central allegation is that "Pfizer, working in partnership with the Nigerian government, failed to secure the informed consent of either the children or their guardians and specifically failed to disclose or explain the experimental nature of the study or the serious risks involved" or to inform them that alternative treatment proven to be effective was immediately available from Médecins sans Frontières at the same facility.

The case could only be brought in the US if it alleged a violation of what is known as "the law of nations." The US Supreme Court has cautioned lower courts to be conservative in determining whether a category of actions contravene "the law of nations" accepted by the "civilized world" as a norm of international law. So for the Second Circuit to permit this case to proceed in the US, it had to conclude that the prohibition of nonconsensual medical experiments on humans has become such an international human rights norm. The court reached the conclusion that the informed consent requirement is such a norm because it is sufficiently "(i) universal and obligatory, (ii) specific and definable, and (iii) of mutual concern," to be considered a "customary international law norm" that can support a claim under the Alien Tort Statute.

The court found that the 1945 to 1948 war-crimes trials at Nuremberg, especially the Doctors' Trial, are foundational. Even though the major war-crimes trial, the International Military Tribunal (IMT), was the only multinational trial at Nuremberg, the court found that the subsequent US military trials, including the Doctors' Trial, "effectively operated as extensions of the IMT." As noted above, the Doctors' Trial produced the 1947 Nuremberg Code, the first precept of which is the requirement for voluntary, competent, informed, and understanding consent of the research subject. In the Second Circuit court's words, "The American tribunal's conclusion that action that contravened the Code's first principle constituted a crime against humanity is a lucid indication of the international legal significance

of the prohibition on nonconsensual medical experimentation." Moreover, the court noted, the requirement of informed consent in research has been widely adopted in international treaties (including the International Covenant on Civil and Political Rights and the Geneva Conventions), domestic law, and nonbinding international codes of ethics such as the Declaration of Helsinki.

The court found that in addition to being universal, the informed consent norm is specific in its requirement and is of mutual concern among nations. On this latter point, the court concluded that promoting the global use of essential medicines can help reduce the spread of contagious disease, "which is a significant threat to international peace and stability." Conducting drug trials in other countries without informed consent, however, "fosters distrust and resistance . . . to critical public health initiatives in which pharmaceutical companies play a key role." The example the court cited was local distrust of international pharmaceutical companies that led to a 2004 Kano boycott of polio vaccination efforts—which allowed a polio outbreak to spread across Africa, making global eradication all the more difficult. Eradication of polio continues to be the number one priority of Bill Gates; he is relying almost exclusively on a universal vaccination strategy in the part of the world that still has cases of polio, including Nigeria. Smallpox was eradicated using pre-human rights forced vaccinations—but this strategy can no longer be pursued either ethically or legally today. Only respect for human dignity and requiring informed consent for vaccination is likely to be successful: force will only breed resistance and failure.

The Second Circuit's persuasive opinion that the doctrine of informed consent has attained the "law of nations" status of an international human rights norm that can be enforced in the world's courts should help persuade international corporations and researchers alike to take informed consent—and perhaps the other principles of the Nuremberg Code—much more seriously.

BENEFIT AND EXPLOITATION

Informed consent is a necessary condition for ethical research on humans, but it is not sufficient. The Nuremberg Code, for example, has 8 additional welfare provisions. The most relevant for this discussion is the requirement that "the experiment should be such as to yield fruitful results for the good of society . . ." [Number 2] and "the degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment."[6]

In the context of research done in developing countries, the 1992 Council for International Organizations of Medical Sciences (CIOMS) Guidelines have restated this by noting 2 important points: (1) there are diseases that rarely if ever occur in developed countries, such that if any research is to be done on them it must be done in the developing countries which have the disease; but (2) in order for research to be ethical and nonexploitive in this setting, it must offer the potential of actual benefit to the people in the developing country in which the research is done. Put another way, in order for research to be ethical in developing countries, the residents of the country in which the research is done must have access to the fruits of the research. The CIOMS commentary to this guideline (Guideline 8) states, "as a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to inhabitants of the underdeveloped community in which the research was carried out: exceptions to this general requirement should be justified and agreed to by all concerned parties before the research is begun." This requirement is designed to prevent gross exploitation of research subjects who, if the fruits of the research were not made available to them and their fellow citizens, would have simply been used for the benefit of the researchers and their sponsors. Nonetheless, the CIOMS guidance remains a bit vague, as the experience and debate surrounding the short course AZT trials in Africa in the mid-1990s illustrates.[7]

The goal of the short course AZT studies was to see if lower doses of the drug AZT than those used in the US could reduce the rate of maternal-child transmission of HIV.[8] It was well established that doses of AZT that cost $800 (not taking into account screening and other related costs) reduced maternal-fetal transmission of HIV by as much as two-thirds in the US. If the developed countries had been willing to subsidize the cost of this regimen, no additional research would have been needed. But because many African countries could not afford this expense, the decision was made to attempt to see if lower (and therefore cheaper) doses would prevent maternal-fetal HIV transmission. Several developing countries were chosen as research sites. The justification for conducting research in those countries was not that the population suffered from a disease that did not afflict people in developed countries, and not that no treatment existed, but that their impoverishment made an existing therapy unavailable to them (as long as developed countries refused to subsidize the costs).

The issue, as always, is to determine the ethical acceptability of the proposed research before it is conducted; ie, to first question whether the research should be done at all. In a case like this, where the researchable problem exists solely because of economic reasons, the research hypothesis must contain an economic component. The research question should have been formulated as follows: We know that a given regimen of AZT will reduce the rate of maternal-child transmission of HIV. Maternal-child transmission of HIV in many African countries is a serious problem, but the effective AZT regimen is not available because it is too expensive. If an effective AZT regimen costs $X, then it will be made available in the country in which it is to be studied. Therefore, we will conduct trials in certain African countries to see if $X worth of AZT will effectively reduce maternal-child transmission of HIV in those countries.

The most important element of the development of this research question is the third part. Without knowing what dollar amount X actually represents, it is impossible to formulate a research question that can lead to any benefit for the people of

the country in which the research is to be conducted. There is no way to determine what $X represents in the absence of committed funding. Therefore, an essential prerequisite to designing ethical research in underdeveloped countries is identifying the source and amount of funding for providing the fruits of the research to the people of the developing country in which it is to be studied as a condition of the research being approved.

If a study found, for example, that $50 worth of AZT has the same effect as $800 worth of AZT, it would greatly benefit the developed world. Developed countries, which currently spend $800 per case on drugs alone, could pay substantially less for this preventive measure, and, because the research was conducted elsewhere, none of their citizens would have been put at any risk. At the same time, if the developing country could not afford to spend $50 any more than $800, then it could not possibly derive information that would be of any benefit to its population. This is the definition of exploitation. It is only recently that developed countries have been raising money to pay for antiretroviral therapies (ARTs) to treat HIV/AIDS in developing countries, and this is an ethical approach to a worldwide epidemic. In the original AZT trials, however, this option was not seriously considered and no one "ensured" that at the completion of successful testing the product would be made reasonably available, thereby violating the CIOMS guidelines. The guidelines say that there can be exceptions to this general requirement, but that exceptions must be "justified" and "agreed to by all concerned parties." It is not clear to whom the exception must be "justified" or on what grounds.

With our colleagues Leonard Glantz and Wendy Mariner, we have previously suggested that the standards for research in developing countries should include the following:[9] (1) There should be a presumption that researchers from developed countries will not conduct research in developing countries unless it can be shown that a direct benefit will be bestowed upon the residents of that country if the research proves to be successful. (2) The person or entities proposing to conduct the study must demonstrate that there is a realistic plan, which includes identified funding, to provide the newly proven intervention to the population from which the pool of potential research subjects is to be recruited. In the absence of a realistic plan and identified funding, the population from which the research subjects will be drawn cannot derive benefit from the research. Therefore, the benefits cannot outweigh the risks, because there are, and will be, no benefits. The "realistic" requirement means that where the health care infrastructure is so undeveloped that it would be impossible to deliver the intervention even if it were free, research would be unjustified in the absence of a plan to improve that country's health care delivery capabilities.

Some might argue that these standards are too strict and that adhering to them would reduce the amount of research that could be conducted in certain countries. The answer, of course, is that if the benefits of the research are not made available to the inhabitants of that country, they have lost nothing by the lack of such research. Others might argue that research in developing countries is justified if it might benefit the individual research subjects, even if it will not benefit anyone else in the population. This is a misconception of the goals of research and a dangerous confluence of therapy and research. Research is, by definition, designed to create generalizable knowledge, and is legitimate in a developing country only if its purpose is to create generalizable knowledge that will benefit the citizens of that country. If the research only has the potential to benefit the limited number of individuals who participate in the study, it cannot offer the benefit to the developing country that legitimizes the use of its citizens as research subjects. It should be emphasized that research with the goal to prevent or treat large populations is fundamentally public health research, and public health research makes no sense (and thus should not be done) if its benefits are limited to the small population of research subjects.

PULMONARY HYPERTENSION TRIALS

"Globalized" pulmonary hypertension trials fail ethical analysis at most levels of justification, both fact and values. First, the disease is not a public health problem in the developing world and does not affect large numbers. If pulmonary hypertension is not unique in these populations (eg, the TRUST study was limited to idiopathic pulmonary hypertension and pulmonary hypertension associated with human immunodeficiency or collagen vascular disease),[10] there is no justification for a clinical trial using a vulnerable and exploitable population when these trials could just as easily be done on subjects in the US and Europe. If the pulmonary hypertension found in developing countries is unique in some way, then the ethical justification requires a realistic plan to provide the population with the benefits after the trial. Furthermore, if the etiology of the pulmonary hypertension in the developing world is caused by preventable infectious diseases (HIV or parasitic infection) or environmental toxins (drugs and pollution) then the focus of research should be to address and/or treat those causes rather than the resultant pulmonary hypertension.

In the context of pulmonary hypertension it might be argued that there are diseases that only affect people in developing countries for which there are no effective treatments, but that the treatments that might be discovered could be expensive. The argument continues that it is not right to fail to develop treatments that could benefit some affected people because they will not be available to most affected people. This objection raises quite a different issue from planned benefit sharing. The impetus for such research is the absence of effective treatment and not the absence of economic resources. We have discussed research intended to determine whether effective but unaffordable interventions would work if used in lower, less expensive dosages. The researchable issue arises from an economic circumstance. The only way such research could offer any benefit is by "curing" the economic problem by establishing that the less expensive form of the intervention

will be affordable and available. Absent knowledge of financial resources, one might well be creating a new unaffordable, and therefore useless, intervention. In contrast, in the case in which one is developing a new intervention, not because of poverty but because no known effective intervention exists and the disease is prevalent in a particular geographic area, the issue is quite different. In such a case one is not conducting research to try to "cure" the effects of poverty but rather because of the need to create new knowledge to treat a currently untreatable disease. However, even this case may raise problems similar to the ones addressed here. If one were to try to develop an intervention for such a condition and chose research subjects from impoverished segments of a society, knowing that only the wealthiest segment of that society could benefit from that intervention, such subject selection would be unethical for many of the reasons we have discussed.

CONCLUSION

The requirements for informed consent and benefit sharing are not controversial. But application of them to particular research projects has not been universal. Research funders who hope that their studies will yield beneficial knowledge may neglect the steps necessary to ensure that the benefits will be made available. Ethical codes have not been sufficiently specific or enforceable to protect research subjects from exploitation. It is essential to replace vague promises with realistic plans that must be reviewed and approved before the research commences.

It is essential that the wealthier countries of the world use their resources, both financial and technological, to help resolve the health problems that afflict the poor of the world. Doing so will undoubtedly require research. But research is a means to solving health problems, not an end in itself. The goal must be to create interventions that will benefit the people of the countries in which the research is conducted. Focus should be on public health and prevention. Developing countries will benefit only if the knowledge gained produces interventions that are affordable, accessible, and deliverable. This must be determined as a condition of approval before research is conducted so that limited research funds are not wasted, and research subjects are not unjustly drawn from populations that will not be able to benefit from the research.

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