REPORT 3

Doing the Right Thing - Globally: The Global Forum on Bioethics in Research - November 7-10, 1999

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Introduction

"It is clear to many people in developing countries that researchers from elsewhere do not come to visit us predominately for altruistic reasons," said Solomon Benatar, MD, head of the department of medicine at the University of Cape Town in South Africa. "There is a widely held perception by many vulnerable people that they are being exploited."

Delivering the opening plenary address to The Global Forum on Bioethics in Research, Benatar maintained that foreign research interest in developing countries is "almost a sweatshop equivalent of labor to produce information that will be of very considerable interest to markets elsewhere." He believes that developed countries increasingly are conducting research in developing ones because the higher incidence of disease in poorer countries reduces development costs, and because regulatory oversight is "not quite as stringent."

Benatar focused on the "enormous amount of poverty at the bottom" and the fact that it is increasing. He pointed to the disparity between the richest and poorest quintiles of world population, which has grown from a ratio of 9-to-1 in 1900, to 30-to-1 in 1960, to more than 70-to-1 today. Most of the world's burden of disease is concentrated in the poorest countries and among people of color. He linked poverty to the emergence of new diseases such as HIV infection and said it was in the enlightened self-interest of the developed world to reduce this breeding ground of pestilence.

"Don't shy away from the complexity," the "enormous variations of how people view themselves," Benatar urged, "how they view illness, how they view health care, and the way in which they see the world around them." He called on the audience to embrace these differences and try to work them into their hypotheses.

The solution to medical problems does not lay in biomedicine alone, Benatar said. "You want to foster the empowerment of people through the type of cooperation that may enhance human flourishing generally, and make the public of developing countries feel [like] essential partners in the process of human advancement in an interdependent manner." Benatar wants to see "a paradigm shift in thinking and action, acknowledging a reciprocal relationship between individuals and society as a notion of interdependence." He used the example of South Africa where there was "a total switch in thinking . . . from might-is-right to right-is-might."

Who decides? Who's to blame?

The days when researchers from one nation could unilaterally undertake a medical experiment upon the people of a less developed nation clearly have passed. Consent is required. But consent from whom? What constitutes consent? And, if one country exploits another biomedically, should the blame be shared?

"We keep on blaming the northern institutions and the developed nations that they exploit our nations and our people," said Nelson K. Sewankambo, MD, dean of the medical faculty at Makerere University in Uganda. "I think that we are also partly to blame because we let them do

so. They don't impose themselves onto countries, we allow them in to conduct their research. And then they go away as they came. We need to reevaluate ourselves so that we can perform better in the future."

Robert Levine, MD, of Yale University School of Medicine, turned to guidelines from the Council for International Organizations of Medical Sciences (CIOMS). They state that the goals of a trial "should be responsive to the health needs and the priorities of the host country." He called this "a more secure safeguard than informed consent." A corollary of the guidelines states that "any product developed should be made reasonably available to the host country."

But often there is a tension between government, society, and individuals. "The interest of the community and the national government does not necessarily always coexist," said the WHO's Srinath Reddy, MD. One discussion group from the breakout sessions reminded the Forum that there have been examples where medical products provided as part of the trial agreement did not go to benefit that nation's people, but were sold by its leaders to a wealthier country.

"It is individuals that are at risk," declared Carel Ijsselmuiden, MD, a professor at the University of Pretoria School of Public Health. "It is completely unthinkable to start playing off community benefits against individual risk. The ultimate scenario would be that a country tries to sell their population to solve their budget deficit."

WHO senior ethicist Daniel Wikler, MD, added, "If the underlying ethical principle is that each individual should be considered sacrosanct and not sacrificed for the benefit of the whole, simply adding a hospital to the community does not make it okay to have ignored the health interests of some of the participants."

But is that a universal principle? Slavery still exists in far corners of the world. The legal and societal status of women in some countries is less than equal to that of men. And many individuals, in a variety of societies, relate to physicians in an unquestioning manner, not as equals in the delivery of health care.

Renzong Qui, MD, a bioethicist from Beijing, explained that in the Confucian tradition of China, an individual is never considered in isolation, "the family is always involved in decision making. The physician provides information to the family and the family decides if it should be disclosed to the patient." And the family must give permission for a patient to participate in a clinical trial.

Qui said that this standard is breaking down as the society becomes more market-oriented and the people become increasingly more self-oriented. Only in 1998 did a landmark legal agreement establish the principle of patient autonomy and informed consent. The court decided to compensate a patient for a procedure conducted without his permission as part of the control arm of a clinical trial.

No "clinical one-night stands"

"We must first of all be focused on the research participants themselves and the community to which they belong," said Leonardo D. de Castro, PhD, an ethicist at the University of the Philippines. "After all, they are the ones who bear the individual burdens and undertake the risks relative to the procedures."

He urged nongovernmental organizations, researchers, and government officials not directly involved with a project's success to assist in "the education and empowerment" of participants. It is important that they complete a trial "without the feeling of having experienced a clinical one-night stand."

"Sometimes the community's expectations are far different from what the researchers' expectations are," said Claudette Francis, MD, who is working on HIV vaccine trials in Trinidad. "Community participation confers transparency to the research." She urged a full sharing of information.

The NIH's Gerald T. Keusch, MD, was concerned that early sharing of data with participants might disseminate incorrect information. He called peer review "an imperfect but necessary process." That brought an immediate response from US AIDS activist Mark Harrington, with the Treatment Action Group (TAG). "We have had to rethink that many, many times in the [NIH] AIDS Clinical Trials Group [ACTG]," he pointed out. "We have gotten to a point where they actually do send out the executive summary of the study to the principal investigator, the investigators in the field, the study nurses, and to the patients. This is before peer review." He said the ACTG has been "pretty lucky" in terms of accuracy of those initial reports.

"But you also have to consider the risks of not letting the information out in that window," Harrington added. "If there is an immediate public health impact, the patients in the study should be the first to get it." Professor Povi Riis, from the Copenhagen Ministry of Science, described how Denmark has been bringing lay members of the community into the review process for two decades, so that now there is parity between scientists and lay members. "The reflections of your local culture will be there from the starting point." Our clinical investigators say that having "the human subjects come and explain what it is like to be a subject is the single best panel," said Ezekiel Emanuel, MD, director of clinical bioethics at the NIH Warren Grant Magnuson Center, "because they had never actually sat down with their subjects and talked to them. They learned much more from that than from people giving lectures."

The "compartmentalization" of communities into researchers, patients, and other discrete groups, "is designed to maintain barriers between the groups," said the WHO's David Griffin, MD. "It leads to suspicion and mistrust. I like to think of the process of community involvement as the democratization of research."

An open agenda, and a wary eye

Cape Town's Solomon Benatar supports a process-driven rather than a rules-driven approach to ethical research. He argued that a technical manual will always have gaps, while guidelines that "outline the spirit" of the research endeavor and the collaboration "could lead to constant improvement." He seeks guidelines that are "more like a constitution open to interpretation, that might play out differently, in different ways in terms of the precise language. But the spirit would play out in the same way."

"Legal solutions or compulsion of any kind is not a good ethical solution," one Forum discussion group concluded. It offered the example of India when compulsory sterilization became part of the family planning program. The community rejected that approach and kicked out the government that tried to impose it.

If you "come to a country with plans already made up, you will get rejected time and time again," said Allen Herman, MD, of South Africa. "You have to come with an open agenda and try and figure out the program with your partners."

Others said that, at a minimum, the trial participants should benefit from access to the results of the study. Benefits can be negotiated upward. It made no difference if the trial was sponsored by a profit-making company or a nonprofit agency, each was greeted with a wary eye and advice to watch out for their own interests.

Bill Hausdorff, MD, director of scientific affairs at Wyeth Lederle Vaccines, cautioned that expansive demands could skew research toward small nations and away from larger ones. Dr. Peter O'Hanley, chief scientist for TAG Immunology and Anti-Infectives Quintiles, warned that one could "kill the incentive [to industry] if the follow-on burdens are too large."

What happens if a trial is not successful? What does the community get then? And what happens if it proves unsuccessful but another trial elsewhere builds on the knowledge gained to create a successful product? What is the responsibility to the initial participants? The scenario is particularly relevant to vaccine trials for HIV, since most observers believe that the initial vaccines will have limited efficacy. No one had ready answers.

Throughout the course of the meeting it became clear that it is advisable to define terms and benefits before the trial starts. That includes something as basic as defining "success" for the trial. A 30 percent rate of protection would probably be judged a failure for most vaccines, but if it were for HIV, some might embrace it as a welcome intermediary step.

Moderator Heng Leng Chee, MD, from the medical faculty of the University Putra Malaysia in Malaysia, offered this summation: "Among other things, ethical standards are also the outcome of struggle and negotiation among the various stakeholders. Community, as however defined, should be empowered to play an effective role as a major stakeholder."

Robbins' rounds raise hackles

"Vaccines present a unique problem to the ethicist," said John B. Robbins MD, a noted vaccine researcher at NIH. "These are medicines given to healthy children who are unable to make informed consent, and who must take these medicines by law. There is no other medicine I know that has these unusual properties." He reviewed several vaccines, explaining how they have brought individual and collective benefit.

Robbins recalled the polio scare of his youth, immediately after World War II. "I remember very vividly, at the end of many summers I was not permitted to leave the house for two to three weeks. Almost all of the children in our community were not permitted to go to the public swimming pools during the hot summer and were not allowed to go to the movies. Every fall when we came back to school there was at least one child with a bad arm, or limping, or one that never showed up again."

A successful polio vaccine changed that virtually overnight. In 1956, when Robbins was studying pediatrics, a New York polio hospital had just closed and 200 iron lung machines were dismantled. Today, critics attack an inactivated polio vaccine that brings disease to one child for every one million births, he said. "This illustrated how scientific advances change our concept of safety and ethical behavior."

Robbins criticized "the notion that a vaccine has to be shown to be effective in various parts of the world." Citing the example of the *Haemophilus influenzae* B (Hib) vaccine, proven effective in the developed world, he charged that millions of dollars were spent and many lives lost on "unnecessary and unethical" additional placebo-controlled trials in developing countries.

"We are all one species becoming more and more hybridized over time, what is shown for some of us is true for all of us," Robbins said. "Countries that do not implement routine usage of all recommended vaccines for their children have governments that should be regarded and treated as unethical." His remarks sparked heated comments from the floor and throughout the meeting. Some questioned his description of the trials in question, others the right of national governments to set their own priorities.

One discussion group argued that data from a trial in a developed country cannot always be applied directly to less developed nations. Sometimes other factors need to be taken into account, including disease burden, and environmental and nutritional differences that might have scientific implications in terms of efficacy. That does not mean that a trial must be placebo controlled; observational studies may be possible.

But Robbins would yield no quarter. For him it was a question of political will. "Only the people with the checkbook have control," he said. "If those countries have million-dollar tanks and 10 million-dollar jet aircraft, they can vaccinate their kids and they should not be let off the hook."

Zulfiqar Ahmed Bhutta, MD, a professor at The Aga Khan University in Pakistan, demurred. "It is a shared responsibility," he maintained. "Countries very rarely have control over their economies in an era of restructuring." He said that institutions such as the World Bank should insist that health budgets be increased.

Securing the future against HIV

Mark Ahn, PhD, senior director for operations planning at Bristol-Myers Squibb, outlined the company's *Secure the Future* program begun last year in southern Africa. It focuses on capacity building in the fight against HIV/AIDS in that region.

Allen Herman spoke of leaving NIH in 1997 to return to South Africa to become dean of the first School of Public Health at MEDUNSA in Pretoria. The school is a partner in *Secure the Future*. A central component of their effort is a distance education program based on the World Wide Web. Students can download their coursework and carry on discussions with fellow students and faculty both by posting comments on message boards and by participating in prearranged chat rooms.

Herman said that the lack of infrastructure and a traditional way of doing things allowed MEDUNSA to "leapfrog what is done in the United States." Even beyond coursework, this technology is helping to create "an electronic community of scholars in southern Africa." He believes that this sense of community will both increase the resource base and help stem the "brain drain" of researchers who often feel isolated.

"We have to train large numbers of people to use the money," Herman said. If you have $100 million and you don't have qualified people, it's important that international collaborations be fostered to promote technology transfer and capacity development to enable local healthcare professionals to efficiently allocate and utilize resources.

Herman identified the lack of linkage between public and private sector review boards as a weakness in South Africa. "Ethics committees are almost sitting in isolation from what is considered to be good practice abroad," he noted. They also "are still struggling with the idea of bringing community people onto our board."

Underlying that is a culture where "autonomy has not become a part of the grassroots of community activism," Herman explained. "It is a nonracial issue, it is about the authoritarian fashion in which South Africa was run. People told black folk what to do." They struggle frequently with this cultural legacy in trying to create a tradition of good ethical practices.

For Edward Kim Mulholland, MD, a medical officer with WHO, one problem with internal review boards (IRBs) is that too often they are viewed as a one-shot deal, to review a trial proposal, rather than as a matter of continued oversight.

"Do we need to train nurses and doctors" as well as researchers, asked the University of Pretoria's Carel Ijsselmuiden. "Yes," he answered, "of course we do. The more training [done], the more likely it is that they will adhere to the protocols. If we look at training from the idea of protecting patients, the more people are aware of ethical practice, the less likely you are to get unethical practice."

It is "crucial to maintain the facility once the study is over. But I think that we should go beyond the facility," warned Wen Kilama, MD, chairman of the African Malaria Vaccine Testing Network. Kilama was concerned about what happens to local researchers and support staff once a study is over. "I would argue that we try to integrate the facility and people into existing structures."

Zulfiqar Ahmed Bhutta suggested framing ethics training in the context of human rights. He urged linking training to decision makers, who "to a large extent are bureaucrats," or they may be political leaders who have no medical training. He supported international linkage because it "strengthens the hand of people who are trying to bring about change. It makes policy makers sit up and listen."

Plans for a cross-cultural bioethics forum

The Global Forum on Bioethics in Research drew together 125 researchers, administrators, and ethicists from around the world on November 7-10, 1999, near the campus of the National Institutes of Health (NIH) outside Washington, DC, in what is hoped will become an annual gathering.

The purpose is "to provide for an ongoing forum for the discussion of issues as they arise," said cohost Gerald T. Keusch, MD, director of the Fogarty International Center at NIH. "Rarely have cross-cultural issues been considered in research bioethics." He sees the Forum as complementing efforts to develop or revise bioethical guidelines.

While the NIH and principal cosponsor the World Health Organization (WHO) intend to remain active supporters and participants, they do not claim ownership of the process. Keusch offered as a model the international AIDS conferences, which have a diverse steering committee and rotating venues.

A secondary objective was to address the need to build capacity for ethics training in developing countries "both at the philosophical level and the functional level." Keusch assured attendees that the "NIH is very committed to helping in the development of a training resource" that is sensitive to local needs and conditions. The third day of the meeting focused on the needs of a "multicentric training program."

People interested in ongoing Forum activities may contact Fogarty Center public affairs officer Irene Edwards at (301) 496-1491 or edwards@mail.nih.gov.

What non-US investigators think of US regulations

How do non-US researchers deal with the US regulations attached to US government-funded research projects? How do they compare with the investigator's own moral rules? And how do the investigators resolve conflicts that arise between the two?

The US National Bioethics Advisory Commission asked Duke University professor Jeremy Sugarman, MD, to report on these and other questions. He visited sites in eight countries--Chile, Guatemala, Haiti, Kenya, Mexico, Taiwan, Thailand, and the United Kingdom--chosen because of

ongoing ties that would allow a quick and inexpensive answer. "We wanted to understand what happens on a daily basis, not what made the headlines," he said. "This is fresh, brand new."

"One of the most powerful messages we saw is that there is a high degree of commitment to conducting ethically sound research," Sugarman reported. "Contrary to the newspaper headlines, people are trying to do a good job and are deeply committed to doing so."

"When there was discordance between the US regulations and local folks' own moral rules," he found, "local researchers and IRB [internal review board] members tended to see these as opportunities for compromise and negotiation. However, these well-intentioned efforts on the parts of investigators often were perceived to be met with a lack of trust by the US IRBs."

"The review process is rather burdensome, time consuming, and often quite difficult despite its importance in doing research," Sugarman acknowledged. The specifics of documentation "posed substantial challenges due to staffing, space, and resources. If you are in a hospital which is struggling to keep the lights on and take care of patients, the idea of keeping records around for 10 years just pales."

Sugarman also encountered "widespread concern that US regulations regarding informed consent placed undue emphasis on detailed documentation to serve foreign rather than local needs. People were doing the job of obtaining consent, but the idea of documenting it on a form, in a culture or society in which paper is never used for birth or marriage--what we consider major events--doesn't seem to make a whole lot of sense" to them.

"In some cases the actual paperwork led to problems of trust in the investigator and sometimes posed risks to the subjects, in that the only people who could read in one country were the guerrillas. That put the subjects at risk."

Sugarman found that there is an enormous desire to learn about ethical practices and "do the right thing." Most non-US researchers have a low degree of familiarity with and access to US regulations and their frequent updates, which "makes it hard to hold people accountable to rules and regulations if copies are not available."

There also was confusion as to which US regulations to follow--HHS, FDA, NIH? "IRBs in this country have trouble with these very same issues," Sugarman observed. "It is not surprising that internationally this raises some concern." Regional ethics conferences "had a very substantial influence" on raising awareness of ethical concerns.

Ellen Hardy, MD, from Brazil asked, "Why should we work by your rules?" Sugarman replied that the study was commissioned to answer a specific policy question "with respect to what happens where the US is funding research in another country." Current law requires that US government expenditures must conform to American guidelines.

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