

**37th Union World Conference on Lung Health:
Plenary: Clinical Trials:
Ethical Issues in High-Burden Countries
November 3, 2006**

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ANNE FANNING: Professor Larbaoui, to my left, is a member of the board and a longtime member of the International Union from Algeria. Professor Larbaoui.

DJILALI LARBAOUI: Thank you very much [French spoken] Canada [French spoken] chairman, co-president [French spoken].

ANNE FANNING: Ladies and gentlemen. Thank you, Professor Larbaoui. And it gives me a great deal of pleasure to welcome to the podium Dr. Solomon Benatar to address you in this 37th World Lung Congress on the subject of clinical trials and the bioethics of clinical trials in high-burden countries. Dr. Benatar, I'm sure, is familiar to many of you, but let me tell you a bit about his background. Dr. Benatar is currently the director of a bioethics center in Cape Town, which he founded and has directed since 1999. He is also the chair of a research ethics board in South Africa and director of an NIH Fogarty-funded capacity building for international research ethics. He, luckily for those institutions in London and the University of Toronto, is a visiting professor on bioethics. But his background after graduating from medical school at the University of Cape Town was a family practice there and very shortly, further training in anesthesiology and internal medicine. And

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throughout his 20 years of chairing the Department of Medicine in his hospital, he has had passions and convictions and commitments on a broad range of areas of interest that impact our areas of concern. He has been an advocate for academic freedom, for medical ethics in the practice of medicine, for engaging humanities, or the medical community in humanities, and for the ethics of the delivery of health care systems and assuring the human resources. He, in fact, in my view, is the voice for social justice for the globe. And it is a great personal pleasure for me to welcome him and to invite him to take the podium.

SOLLY BENATAR: Good morning, everybody. Thank you very much, Anne, for that very warm introduction. And also, thank you very much, indeed, to the organizers for inviting me to speak at this plenary session and for giving me an opportunity to be present at this important congress on which I've attended on only the odd occasion in the past.

Now I want to begin with a sort of overview of what I want to do today and to explain what it's about. So if you can follow the kind of threads that I want to draw together in talking about the ethical issues in clinical trials in developing countries. I want to point out that this began with a growth of clinical research. Clinical research has, in many ways, become an industry, a powerful and a big and an

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expansive industry that has very rapidly over the last 10 or 15 years spread into developing countries. And I'll just spend a few moments on that. Then I want to say a few words about the world as it today, a globalizing world in which we are all interconnected. And I'd like to spend a few moments on that because I think that those of us including myself who've had the privilege of having almost everything we need in our lives don't necessarily understand what it means to live like so many other people in the world. And certainly, if that applies to me, living within Africa and certainly for many years until I became sensitized to those issues, it applies even more for people who come from other countries to do research in developing countries without an understanding of the context in which that research is taking place.

So those are some of the issue I want to begin with. I then want to turn very briefly to HIV/AIDS as a turning point in clinical trials. There's something that happened with HIV/AIDS that I'll mention very briefly that sparked an enormous debate about the ethics of clinical trials and developing countries. And that will lead me into talking about some specific ethical considerations in clinical trials and developing countries or high-burden countries or whatever you want to call them. I put developing in records because I think all countries are developing. If I have to look at the

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shortcomings in any society in the world, I can find them, including those who consider themselves to be the most developed. It also means the most rich, but that doesn't mean so developed in my county, so I'm putting developed [inaudible].

Then I want to come to some disagreements in the research ethics. These disagreements were [inaudible] debated over the rewriting of the Declaration of Helsinki and the rewriting of the CIOMS Guidelines in 2000 and 2002. I participated in some of those discussions and it was a harangue [misspelled?] with the views of people from developing countries not adequately heard, but some of those points are coming to the floor today and I anticipate they'll be heard more profitably.

And that will lead me then into some conclusions around which I hope you will ponder and think about in particular if you are involved with undertaking clinical research in developing countries.

Now, this is just a brief summary of some data that was published in [inaudible] a few years ago. I haven't managed to get updated information on this, but I imagine that those trends that I am showing you here have increased enormously. So if you look at the preclinical testing of drugs in animals in the 1995-1998 period, there was a

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significant increase in that sort of research. If you look at enrollment in multicenter trials, that has increased by over 200-percent during about a 10-year period. The number of overseas investigators, and that means collaborating research records in developing countries also increased enormously. Many of those people were just sort of passive kind of partners in the research. And that's been part of the problem because they haven't adequately participated in enter clinical trials themselves. But, more important, what we need to understand are the forces that are fueling the clinical research. Most academic centers throughout the world including those in developing countries are more dependent than ever on industry funding [inaudible] research, and of course industry is interested in doing large trials and they want to reliable results very rapidly in order them to enable them to register their drugs and market them and reap the profits from the investment that they have put into developing those drugs.

And then, of course, there's always been a concern about easy access to developing country subjects who have very enlarged numbers, any disease that you want to study that takes place in the developing world. There are many more in the developing world that one could study. And until recent years and perhaps even still today, the research

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ethics committees that review the protocols for that research are on a powerful list who have been educated and more likely to pass a research party that might not as easily be approved elsewhere.

So this is the background to the growth of an industry. The growth of the number of people and the number of products that [inaudible] to developing countries in order to test them and then to take that knowledge back for profitable purposes and for treating peopling in developed countries and throughout the world. Now, this graph that I am showing here - and I apologize to those of you who've heard me lecture before, I show this graph in many lectures - shows the distribution of world income in 1990. And what is show is if you divide the world into quint files [misspelled?] of population, in 1990 the richest 20-percent of the world's population was 60 times richer than the poorest 20-percent of the world's population. And the distribution of the money is shown in that income slide 82.7-percent, the richest in 1990, with the other figures going lower down.

Now, the interesting thing about this is this has occurred with phenomenal growth of the economy. The world economy has grown by five to seven times over the last 30 or 40 years, massive growth of the global economy. But if you

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look at the distribution of that growth, you will see at the beginning of the century, in 1900, that the ratio of the richest to the poorest was 9:1. That grew to 30:1 by 1960, to 60:1 by 1990 as the shape of the glass shows, and by 2000, 82:1. So what's happening is the glass at the top is growing broader and shorter and the stem is growing narrower and longer. And in fact, instead of the resources trickling downwards, in many ways it would seem as though the resources are actually funneling upwards. To maintain economic growth in the developed parts of the world, first the amounts of human and material resources are continually extracted from the developing world.

I show this slide because all of us in this room and all of us who undertake the nickel [misspelled?] and all of us who have had the privilege of the kind of education that we have are in that top 20-percent. And I want to suggest to you that we don't necessarily understand who people at the bottom end of that stem, many of whom are our research subjects, see the world and how they see us. And I were to say that in many ways we're almost oblivious to the needs and the lives of those people and probably don't care a great deal about them, not you and me, but the world in general in the way it uprights. And I would ask myself why those people should care about us and why we should be safe and secure in

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the kind of world where we have everything we need and much more and some people don't even have the basic requirements to exist. So I want us to be sensitized at this very early stage to this is the global world.

This is the context in which we undertake research. Would we go from our privileged positions, my privileged position in my country, your privileged position in your countries, into developing parts of my country or elsewhere? We come with a whole baggage of what we expect from life, and what we think is important, and the way we view people and the world.

Now let me view very briefly, and I don't want to dwell on this, but these are issues that are not often discussed, but I do want to raise them here. I want to ask why people are poor. Why does poverty continue? Why does poverty that is so crucial to dealing with epidemics like tuberculosis and HIV and everything else, why does it persist? And I want to suggest to you, as I've done already, the economic growth of the wealthy takes place at the expense of the poor largely, maybe not deliberately, but that's the way the global economy is organized. I'm afraid trade rules advantage the wealthy. And just to give you one example, the farming subsidies in the UK and Europe are \$350 billion a year and trade protection is next. It costs developing

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countries about \$50 billion a year in lost income. The maintenance of developing country debt is another issue. They are eager lenders, especially in the '70s, when there was a lot of money around. There were a lot of corrupt borrowers and a lot of that money was linked to arms trading. In fact, from 1980 to 1994, more than 60-percent of economic aid given to developing countries was spent on acquiring arms in those countries. So the money flew back directly to the arms producing countries. Many people don't appreciate that and don't appreciate the corruption that's involved in selling arms to despots and kleptocrats. The annual interest paid on [inaudible] Africans exceeds by about tenfold, \$21 billion a year foreign aid to Africa.

So the foreign aid that's given to Africa is miniscule in relationship even just to the interest on debts removed from Africa. Poor governments in corruption, I don't want to underestimate that. It's a major problem in Africa. We have an enormously long way to go in Africa, and I presume in other developing countries, to have the kind of democratic and socially democratic governments that we desire. We are processing through that transition phase, and so I think that we have a long way to go. But I do want to suggest to you that powerful nations are complicit in supporting despots and kleptocrats who sale their country's

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assets to arm and enrich themselves. And you have to look at the armies that they have to protect themselves to remain in power and ask yourself where they got those weapons from. They certainly weren't manufactured in developing countries. And this continued extraction of material and human resources, oil, diamonds, and platinum, around which many wars continue to be fought and recruitment of health professionals without any recompense. Developed world countries have no hesitation in recruiting nurses and doctors from developing countries and not even attempting to pay back a portion of their educations into those developing countries. I can't imagine that we can do that without some degree of conscience.

So we've heard about the two million people that die every year from tuberculosis. I think it was 5,000 a day who die from tuberculosis, and it's a treatable disease at minimal cost. What about the 34,000 children under the age of 5 who die daily from hunger and preventable disease, easily preventable diseases? And there's no shortage of food. We don't need GM crops. It's only in the distribution of food and who controls the distribution of food that ensure that people remain hungry. Fifty billion dollars could prevent 50-percent of premature deaths, and that 0.2-percent of the combined GDP of affluent countries. The Iraq war has,

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I think, cost over \$400 billion and rising. I saw a figure the other day predicting \$1 trillion or perhaps even \$2 trillion ultimately spent on the Iraq war, and the WHO annual budget is a couple billion dollars. I want to suggest to you that there are no successful solutions to global health to recurrent and new infectious disease pandemics and multidrug resistance if the forces perpetuating poverty are ignored. We have to understand those [inaudible]. We have to address those at the same time as we continue with all the wonderful scientific work we're doing, all the marvelous clinical activities and endeavoring to bring drugs and treatment to many people. But if we consider those things only and forget about the upstream way and with the global economy upright, if there's no attention paid to that at all, my anticipation is that we will run out of [inaudible] steam and that all the things that we've started doing under emergency conditions today are ignitously [misspelled?] lost into the future.

So that's the background, in a sense, against which we need to consider the ethics of clinical trials, but let me give you just one or two other points. I want to suggest to you that not even science is value-free. In the 1990s, two-thirds of the United States expenditure and 40-percent of UK research and development expenditure was spend on military research. Military research is the most important area that

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consumes research workers than any other people, the importance of weapons production and war. Ninety-percent of medical research expenditure is on disease that account for 10-percent of the global burden of disease. So many of the questions that researchers have been asking until recently have not been determined by the questions that need to be answered, but rather by whether there's somebody willing to pay for the questions to be answered, which means of an industry. And in fact, about 50-percent or more of the global research budget comes from the pharmaceutical industry. So as a result of this, the interest of researchers can often outweigh the interest of research subjects. Researchers come into countries because they want to pursue particular problems. They are not particularly interested in what the research subjects want perused. And requiring new knowledge is valued more than applying existing knowledge. We have libraries full of existing knowledge and which could be applied which is not applied. For example, the application of knowledge in the '60s and '70s that could have irradiated tuberculosis that was never applied for lack of a vision to accumulate and distribute the resources necessary to give treatment to everybody. And I want to suggest to you that saving lives in poor countries is not dependent for dominant [inaudible] medical research. It's

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dependent on many, many other things, but of course medical research and new forms of treatment and new diagnostics make a major impact on what we're doing, and so hence the need for clinical trials, hence the need for more research, but not in isolation.

So those are the issues that I want you to be conscious of as we move into the main topic of today's presentation. Now, I want to suggest to you that in the HIV/AIDS era a lot of things happened. First of all, the need to avoid stigma became very prominent. The idea that people with an infectious disease like HIV would be stigmatized became so powerful that human rights issues overemphasized anything else. The public health concerns of notification of HIV-positive people; all of those considerations were overridden by the need to avoid stigma and to protect individual human rights. And, of course, issues of justice began to arise at that time too, which are not prominent issue in the ethics of medical research. If you look at the early declarations of Helsinki and the early CIOMS Guidelines, there was nothing very much there about justice and human rights. Avoidance of exploitation became a dominant concern because it seemed to many people, especially those of us in developing countries, that much research was exploited but came to take advantage of what could be done in

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developing countries without any concern about whether that knowledge would ever be applied to the benefit of the people who were the research subjects.

This arose in particular in relationship to HIV studies and in particular when anti-retroviral therapy [misspelled?] became available. Should post-trial treatments be provided for those who became positive during the studies or identified as being positive during the studies? Very, very hot debate that I'll come back to a little later. And of course, the use of placebos was very hotly debated around the ACTG 076 studies done in France and elsewhere where [inaudible] rather expensive and long regimen. It was possible to reduce mother-to-child transmission of HIV, a regimen which was not applicable in developing countries not only because of expense but because of demographics of who a woman presents just shortly before labor to deliver their babies and are unable to stop breast feeding.

But the placebo studies that were done came under enormous fire from somewhat imperialistic ideas of research ethics from the developed world. Those ideas are gradually changing. We're beginning to understand the debate a bit better, and I'll explicate that for you in the course of today's discussions. And then, of course, there's the whole concept of benefit sharing, some way of sharing the benefits

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of research in an appropriate manner with those who are the subjects of research. So these are the specific ethical issues that I want to discuss a little bit more.

First, I want to discuss something called the Standard of Care, which has been a hotly debated issue and which is slowly evolving. And what we are witnessing here is something that I'm going to call moral progress. We tend to think of ethics as being not only universal, but static, ethical principles, which don't change over time. Our ethical understands as being fixed where science makes progress. I want to suggest to you that as we understand the world better and as we understand the ethical dilemmas better, we can also make moral progress in our understanding of what needs to be done. And I'll explicate some of this around the idea of the Standard of Care. I'll also say something about Informed Consent because Informed Consent is the cornerstone of clinical research. It is the most important clause, if you like, in the [inaudible] code following the atrocious experiments that were conducted on humans during the second World War. And yet, our attention to Informed Consent is highly inadequate even today.

I'll mention briefly the importance of balancing consideration of benefits and harms and the development of partnerships because medical research today cannot take place

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just with medical researchers. The world is too complicated. Health issues are too complicated. Doctors and scientists can't work alone in undertaking research in developing countries. The social and other issues that involved require multi-discipline routines and partnerships. Then I'm going to move to resolving some disagreements in research ethics. And I'm going to try to resolve those through proposing that we need to understand the people that we work with through other perspectives if we're going to resolve some of those dilemmas. And I'll give you some other background to those dilemmas a little later. And I'm going to conclude by suggesting that we knew new paradigms of thinking for advancing health through research, not just acquiring new knowledge but actually advancing health through research because after all the reason we do research is not just to have the knowledge, but to be able to use it.

So let me come to the Standard of Care as the first topic I want to discuss. Now, the HIV transmission prevention studies that I mentioned sparked off an enormous debate on whether placebo could be used given the evidence of the effectiveness of ACTG 076, which was a prolonged course of treatment prior to first delivery. And there were contrasting views about that and great concern expressed about double standards, that there should not be double

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standards in ethics. The ethics of conducting a trial in the developed world should be the same as the ethics of conducting a trial in the developing world. And I don't disagree with that. I think that there are universal standards that can be applied, but without considerations of context, it's not possible to apply universal standards without understanding the context in which you're attempting to do that. But the debate between single universal standards and some sort of local standards, and I won't go into that debate in detail except to say that I reject the idea of local standards being determined purely on the basis of what's available in particular societies. We have to get beyond that.

But of course these were the issues that were discussed in the Helsinki Declaration and in the CIOMS Guidelines, which were not solved. They were not adequately solved, but I'll come back to that. So at the time that this debate was taking place a broader conception of the Standard of Care began to evolve. The now the Standard of Care at the time of the ACTG 076 studies related purely to whether or not you could use a placebo in a developing country because the Standard of Care was a term that referred to the standard that was given to the group that would be compared with the new treatment.

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Now, the broader conception of Standards of Care evolved in two papers, one in the *British Medical Journal* - I'll provide the references for you later - and one in the *Journal of Medicine and Philosophy*, and a third paper in a journal called *Bioethics* with the whole concept of equipoise was examined much more closely, and the ideas that had been presented by [inaudible] *Journal of Medicine* Editorial [inaudible] the placebo-controlled studies in developing countries, but turned on their heads by a better understanding of what equipoise meant in its broader sense. And subsequent to that, there has been work on justification for a new conception of Standard of Care and international duty of care and the duty of benefit sharing, and those are the issues that I want to go through with you very briefly.

Now, what is the broader universal conception of the Standard of Care? If we want to do research in developing and we want to have a standard that applied in the same way to people in developing countries as it does to people in developed countries, what could we ask ourselves about the basics of that Standard of Care? And I want to suggest to you that they are as follows:

First of all, respect for the dignity of all subjects anywhere, and that's an important issue. I didn't mention in that champagne glass that I showed you and in that stem is

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that most of the people in that stem are people of color. And there is regrettably a curve of sense of attitudes towards those people that makes their lives mentally less from the lives of other people, those of us who are privileged. Nobody expresses that. It was deeply expressed in [inaudible] era, and the [inaudible] era, and the [inaudible] that, but at the more [inaudible] level, there's not the same concern shown for those people as there could be. And I'm afraid that if we really want to respect the dignity of all people, if we claim to have a universal declaration of human rights, we should be aware of that when we undertake research on highly underprivileged and vulnerable people. [inaudible] is a [inaudible] Informed Consent.

Now, Informed Consent is not just a legal concept, it's a moral concept. It's a concept of a decision that's shared between the researcher and the subject. And how do you tell somebody about a trial and share information about that trial and obtain voluntary consent if you can't address your researcher in a linguistically and a culturally appropriate manner? How much resources are spent on providing the kind of interpreters and anthropologically trained people who understand the culture of those on whom we undertake research? Minimal. Vast sums on some of the

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scientific equipment, but minimal spent on obtaining Informed Consent.

Those who witnessed Informed Consent in many developing countries are often shocked at the extent in which it's a perfunctory process. But yet, Informed Consent is supposed to lie at the center of the ethics of clinical research. So if we want universal standards, surely we should be as worried about how we get informed consent as we do about which drug to conclude in the alternative arm.

The third principle is to undertake research in the best interest of subjects relevant to their needs. It's no good undertaking research of a society, studying a disease that affects them, but for which that treatment will never become available to them. And can we do research if we don't provide some health care? If we're doing research on HIV in Mohave, and your research subject happens to have tuberculosis or malaria, there's no national health service to refer that person to. Can you undertake research and say, "Well, look, I'm just here to do research on HIV. I can't be concerned about the malaria, or your tuberculosis, or your diarrhea, or your diabetes?" Surely research in developing countries should be some way linked to provision of health care, which is a problem I can see. And there needs to be fairness in distribution of the risks and the benefits to

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individuals and the communities. And a much more detailed assessment of what those risks and what those benefits might be.

And then the research must ultimately have a potential for community benefits. And I want to suggest to you that if any group of people were to undertake research in any developing country or high-burden country for many years at a time and there was nothing left behind in terms of raising the Standard of Health care in that society, then there would be something wrong with that research endeavor that was merely interested in acquiring knowledge without insuring that some of that was put into practice and better health care systems.

Now how do we justify this broader International Standard of Care? And I want to offer you very briefly several different levels. We could justify it on a moral level. We could say, "Look, we need to link moral progress to scientific progress. We shouldn't just be concerned about scientific progress." And if we look at things like malfeasance and the moral repugnance that many people have for deprived conditions, that should drive us to want to raise the Standard of Care. The principle of do no harm on non-malfeasance would want us to minimize exploitation, to make sure that we're not just taking but we're giving too.

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And the idea of justice, the other important ethic for principle, would require that benefits and burdens are fairly distributed, so merely attending to those issues would be a moral justification for a broader standard of care. But at the cultural level, we should respect the dignity of difference. People are different. Often we don't like what is different about people but often what is different about them is important.

And we should understand that research invades other societies. It imposes external norms, some of which are beneficial but not all of which are. It raises expectations of care by people. And people in developing countries don't know that a researcher is not a doctor also who is concerned with their care. So the idea of coming into another culture and being seen by them as a doctor from another wealthy country who might have something to offer them, not just a research subject but as a person who is ill and needs something. We need to be aware of those issues. And I think that that should drive us to a higher standard of care.

At the strategic level, there's a long-term self-interest of all in undertaking collaborative work. If we work together with our research subjects and if we enable them to improve what they're doing, there's a long-term self-interest and that makes the subsequent trials easier and if

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means that they will benefit more and the benefits will be shared more adequately. At the operational level, it's part of a capacity-building progress so that we leave something behind when we've gone away, and it also can provide a link between research and improved care. We can show visibly through the research project that research is not just about acquiring knowledge, but also about improving care and it could demonstrate that and you can begin it into practice, then that can role through when the research is over. And then, of course, professional integrity is preserved because there are considerable conflicts of interest between being a researcher and a caregiver. The primary role of the research giver is different. Researcher is different from the primary role of a caregiver. And there often are conflicts of interest that are not easily resolved if one is playing that role rolled up in both. And nevertheless, those are issues that I think do need to be addressed.

Now, one of the steps towards improving a standard of care, how can we do this? What I suggest is that we should involve the community and study design and to determine the specifics of what the standard of care would be in a particular society. There must be a negotiation right up front, not just the plunking of a protocol on somebody's desk

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after it's been thought through in New York or [inaudible] or anywhere else. We need to form partnerships in collaboration, and I'll come back to that in a moment, because undertaking research in developing countries is much more complicated than just doing the research itself. And as I indicated earlier, we need to integrate research with care for other disease.

Now, let me just give you a figure that we calculated some while ago that we knew was an intense debate where in HIV vaccine trials that we should be considering anti-ritual [misspelled] viral therapy to those who might convert to positive during the study. And most people said that it just would be too expensive to do that. But we calculated that in a trial of 8,000 participants with 100 endpoints of HIV infection at \$150 per year, which was the price of anti-ritual viral therapy in April 2004 that would raise the cost to about \$150,000 U.S. for 10 years of treatment. And that's equivalent to 0.4-percent of the cost of a trial. It doesn't sound like too much to add to the cost of a trial to be able to guarantee post-treatment research. Trials are enormously expensive, and these large trials like this are enormously expensive to conduct. One can add something to those very easily. And then one needs to strengthen the infrastructure

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and build capacity and it ensure benefits, as I've indicated on several occasions.

Now, here are three examples, which I won't spell out for you in detail because of time, but there are three studies, the HIVNET 012 study in Uganda, the HPTN trial Lilongwe, Malawi, and the MRC trial in Mwanza, Tanzania, where the research project was rolled into some aspect of health care and where at the end of the trial treatment was extended to communities often through collaboration with other people. So, for example, the Elizabeth Glaser Pediatric AIDS Foundation played a prominent role in the Uganda HIVNET study. And the Lighthouse project facilitated the provision anti-retroviral therapy for research subjects in the Malawi project. So that's the kind of partnerships that I'm talking about. So those cases are detailed in much more detail in one of the presentations that I'll mention towards the end.

What are the lessons that we've learned from people who've undertaken those studies in developing countries and who we've thought about these issues with? And we've learned that integration of health services is the key to improved standard of care. So, for example, if you link antenatal care to voluntary consent and treatment, if you link STD services to VCT, if you have joint coherent management of HIV

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and tuberculosis. If you link those things. If you have horizontal kinds of services rather vertical services and you integrate the health services and if the research is undertaken in a way that it facilitates the integration of the health care services, those are very important lessons. And the partnerships again enable the improvement of the infrastructure.

What do I mean by partnerships? I'm suggesting things like establishing links with other donor aid organizations from ones own or other countries, and I've listed some of them here. Any new research worker from the U.S. or the UK who goes to Malawi or Tanzania could quite easily have found out before they went there which are the aid organizations from their own country that are operating in that county. They might be able to find out what they're doing. They could share information. They might find that they've got overlapping interests. It's possible that there may be some resources that could be coupled to the research to enable the additional aspects to be undertaken that I've indicated to you that the research funding itself would not pay for. It also promotes multidisciplinary and strategic alliances and approaches to systems, whole systems in a county, not just to the linear problems that we often address in the research context. And of course, it enables us to

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involve the host government to get involved with the ministries of health in the countries in which we do research so that we have not only their approval for research we conduct, but also some understanding of what the implications might be for their own health care system and what kind of negotiations they might have to think about undertaking well in advance if they want to introduce those advances from the research into clinical practice.

What are the values of partnerships? First of all, it promotes respect for co-investigators by involving them in the design and conduct of trials. We learn from their insights while they learn from ours. We build their capacity while expanding our own capacity and not least our own capacity for understanding the complexities of other societies. It allows research to improve health care by improving facilities in health care clinics. And again, the money doesn't flow from research projects into that, but it can flow from the partnerships. It enables transition from research into practice.

And it promotes again the kinds of strategic alliances that are necessary for there to be some sustainability within the system. And of course it helps to create a reasoned middle path between pragmatism and unprincipled practice, which turns out to be the lowest local

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standard and unachievable utopias, which are the highest global standards that some aspire to, which is wonderful to aspire to, but which we can't let the failure to achieve prevent us from doing anything else. We do have to strike the middle ground and find out not only where that middle ground lies, but also whether we can use that middle ground to ratchet upwards in a progressively improving world.

So let me move to informed consent and let me suggest a few things. Trained researchers of the same culture and language group should be responsible for obtaining informed consent, increasing the people or accepting that. It is not yet written into the Declaration of Helsinki and CIOMS, but it could be. We need a legitimate informed decision making progress that requires the ability to overcome culture and linguistic barriers of which there are many. Communication skills and trust are essential. And I want to suggest that informed consent is a more complex issue in high-burden countries for many reasons.

I won't go into the potential benefits for research [inaudible]. I just want to highlight a few things. We tend to forget that the benefits of research of the profile of the research worker isn't what they get out of and the profits that can be made from research. We focus off and on that we're doing this for individuals in communities, but we don't

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often focus on what we're doing for ourselves. And similarly when we think about the protectional homes or research, we don't think enough about the psychosocial risks. We might think about the physiological risks, the inconvenience, the participation fatigue with lengthy research, the stress related to culturally unusual medical research and concepts, and raised expectations.

And for community, the stigma and the exploitation due to impoverishment and lack of familiarity with research methods. We have to understand those potential harms. We have to strike the balance between harms and benefits. Now at the end of writing the Helsinki Declaration, and at the end of the discussions on the CIOMS Declaration, Ruth Macklin, a very thoughtful philosopher who participated very deeply in many of those debates wrote a paper in the *Kennedy Institute of Ethic Journal* saying that there were four areas in which people generally agreed, but within each of those four areas there were profound disagreements. And she ventured to suggest that those ethical disagreements would never be resolved. So let me show you what those were and let me see if it's possible to resolve some of the issues that she thought were not resolvable.

First of all, she said research should be responsible to the needs of people in the community studied, but the

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problem is how are decisions taken about what research to undertake in developing countries and how are these prioritized? No agreement on that. Everybody agrees that research is needed on diseases that occur frequently in poor countries, especially when these cause high mortality and morbidity, but no agreement on what sorts of study designs are acceptable, can placebos be used, and what comparative arms should be included. Everybody agrees it's unethical to exploit the vulnerable, but what specifically does it mean not to exploit people? No agreement on that. It is unacceptable to lower the ethical standard of research in developing countries. Everybody agrees on that, but what is the standard of care that should apply in research of the developing countries? How is this defined and justified?

Well, I've dealt with that part already because it was the one that lead into this whole debate, so I won't deal with that again, but let me briefly go through the others. And let me suggest to you that the only way we resolve these issues is by understanding other people. If we try to see everything through the lenses of our own world view, we won't solve those issues because we are too fixed in our viewpoints. I want to suggest to you that understanding others is essential in a globalizing world. It amounts to something that's being called structural empathy. We have to

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have an empathy with the structure of the world and the structure of the environments into which we go. We must understand what they mean and what their implications are for the people who live there. We need to cooperate with each other and have dialogue intelligently. And in order to do that, one needs to critically examine oneself. One needs to understand where one's own traditions come from, what one's own value system is about, what its limitations are. We need to see ourselves as bound to all other human beings. We have to try to imagine what it's like to be in the position of someone very different from one's self, not an easy thing to do. Participatory evaluation is required. We need to deeply listen to other people.

One of my African colleagues that I work closely with says that Western people have got big mouths and small ears, do a lot of talking, but not much deep listening. We really need to listen. There are some profound things that we can learn from seemingly uneducated and underprivileged people in developing countries that have a profound ability to cope with life in a way that we don't. If we listen to them and understand, we can be enriched ourselves. We have to listen. I mean even emancipatory framework. When we undertake research it must emancipate people. It mustn't oppress them. It mustn't be imperialistic, a freedom to use their own

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potential. That's a requirement. Now if we do that, and let me suggest to you some solutions.

How are decisions made about what research to undertake in developing countries and how should these be prioritized? I think the solutions can be found in the following: Clinical trials in developing countries should be relevant to host health. The design and conduct of trials should involve members of the host country. Prior evaluation should be made of whether the study findings can be and will be incorporated into the local health care systems. And these processes involve the kind of dialogue and collaboration from the earliest stages of research design, and there are in a sense analogous to the idea of democratic deliberation and could assist in explicating and justifying priorities in particular contexts.

What study designs are acceptable? Can placebos be used? Everybody looks at the Declaration of CIOMS or Helsinki Declaration and say, "Can I use a placebo or not?" I want to suggest to you that you cannot deduce from guidelines the valid use of placebos in every conceivable setting. They're broad guidelines. They're not detailed rednips [misspelled?]. Application of abstract universal principles in local context requires moral reasoning. You want to read a constitution you need a constitutional judge

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to help you to understand what the constitution is saying. Ethical guidelines are much the same. You need people with bioethical expertise to understand what the meaning is behind some of those clauses and the guidelines. And I want to suggest that the justification of a placebo arm requires careful consideration of harms and benefits of studies designed to ask and answer specific questions in specific context hence the contexture importance in which the research has been undertaken. And each study should be considered on its merits.

What does it mean to exploit? Philosophers have written whole volumes on exploitation without providing a solution. My solution is on this slide. It means taking advantage of power differential to do what researchers want to do without consideration of harms that may be perceived by research participants. Perceived is important because it's not just the harms that you can measure, it's the harms that we can't measure because we don't understand what are perceived as harms by other people. Signing a consent form may be perceived as a harm because of the history of having signed away land on a form. We don't understand that. We may not understand why people are reluctant to sign an Informed Consent form. If we use research subjects as a means to achieving the ends of researchers that's advancing

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knowledge, then the benefits of research will not be fairly available to research participants in the communities. If we're using people as a means to an end and not as an end in their own right, that's exploitation and again undertaking studies in which minimal benefits will accrue to participants and large benefits may accrue to research sponsors in the longer term. And of course denying participants post-trial use of therapies identified as beneficial in environments where such treatments would not otherwise be available.

So let me conclude - I want to suggest to you, and this would be in the thrust of my talk, that research does not take place in a vacuum. The fact that you might be an exquisitely trained research worker, deeply thoughtful, deeply knowledgeable, highly trained, working in a very sophisticated country with the best methodology, and the best resources, and the best team of research workers in the world, doesn't mean that you can understand the whole problem that you're going to research in another institution in another country. The issue is much more profound, as I hope I've spelled out to you be it so briefly in this presentation. I think researchers should understand more about the sociopolitical context in which they conduct studies. They should understand how the health care system operates in a country that they go into. They should

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understand how the power structures operate. They should understand the general conflicts. They should understand how their work might ultimately be best put into practice. Without that sort of understanding, they actually go into societies rather ignorant.

And I would suspect that if some of the developing countries people were to tell us what they thought of us, they would think we were very naïve, that they would like to tell us that they think that we're wasting our time, but more polite than we are. But I think if we ask people of what they think of us in the developing world, we would get some rather rude shocks. Researchers need to understand the different worldviews of their subjects, and that's a whole talk in its own right, which I would like to give on another occasion.

And we need to understand that the perceptions and meaning of medicine and research held by the poor and vulnerable subjects are different of the perceptions and meaning of medicine and research that we hold in highly privileged societies. I've said already and I'll say it again, scientific progress should be linked to moral progress. If we're proud of scientific progress, we should be equally proud of moral progress of doing things in a morally justifiable way increasingly. Partnerships and

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strategic alliances are essential for progress. I don't think that progress could take place without that. And I think the standard of care, whatever it is in that middle ground, if it's not as good as the top end of the scale if we can progressively ratchet it upwards by linking research to improved health care services, then the research procedures will ultimately ensure benefits to participants in a community it will enhance the local capacity for sustainability, and the translational efforts will be taking place [inaudible].

Well, I hope I haven't gone on for too long and I hope I haven't been too provocative, but I hope I have stimulated you to think about the idea of clinical trials in developing countries that goes beyond what read in the Declaration of Helsinki or the CIOMS or any other guidelines. Doing research in developing countries holds an enormous responsibility. And it's only my understanding that people that you do research with you respect them as equal partners having great concern for the dignity and future health of people in those societies that we in the privileged world can really justify ethically undertaking studies in other countries. Thank you.

[Applause]

ANNE FANNING: Thank you, Dr. Benatar. I don't want you to leave the podium because I know that you have presented us with an enormous challenge to look at ourselves, and I'm sure that there are questions and comments. And I'm going to ask for those who have a question or comment go to the microphones in each of the isles and I will ask you one by one. Don Henderson?

DON HENDERSON: Thank you very much, Solly. I think that you have delivered to us what we need to hear in this organization, and you can be sure that we have an interest to act on what you've said. The question is, how should we act? Can you give us some advice as to where we should go and what is the way forward for us?

SOLLY BENATAR: Thank you, Don. I think that your own interest in creating an ethic advisory group within the union and beginning to move down the path of: A) Looking at your own work critically and B) Through that process expanding education within the union is the right way to go. My view is that unless we understand what is right and know what is right through debates and discussion, then chances of doing what is right is going to be less than if we don't know. So I think that knowledge is important.

And I attended the first ethics meeting of the ethics advisory group that you had set up under the chairmanship

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Professor David Miller and we had a very interesting afternoon. I think that group is making excellent progress. We are at the beginning of a learning curve in a sense. It's in a sense starting out as a sort of policing body if you like, which is what ethics advisory research groups are about, but the role is much broader than that. It really is educational. It's a sense to advise people, to help people to understand what the ethical issues are because ultimately ethics is dependent not on people being forced to do what they don't want to do but wanting to do things because they understand the merit of doing it in that way, and that's what ethics education is about for me. If we understand how to think about ethical issues, if we know how to mount the arguments, if we know how to contest the flawed arguments of others, we can make moral progress and we can make wise decisions. It is a long and difficult process.

Scientists and research workers are skeptical to research because they think it's not as pure, as clean, and easy to follow as scientific issues, but in fact there's lots of progress that can be made. And in South Africa, through the generous donations and funding provided by the NIH, I've been running a program to build the capacity of research ethics committees in Southern Africa and in the last four years we've trained 49 people who have played key roles in

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ethics committees around the country, chairmen of ethics committees, vice chairmen, and members of various committees. The whole ethics evaluation process in our country is being transformed through that educational process. And we have another four years of funding and we'll train another 40 or so people. And we'll [inaudible] the capacity to make then make that sustainable.

Now, I think that's what you're embarking on in the union, so you're doing the right thing and I think you could pull in lots of help from many people. Certainly, I'm willing to do whatever I can to assist you, but there are many others who would as well.

ANNE FANNING: Are there other questions or comments?

KENT: I have one.

ANNE FANNING: I'm sorry, Kent.

KENT: Thanks. Solly, thanks again for another enlightening session. I listened to you all day. Getting back to making these recommendations a reality: One of the concerns I have is that the traditional funding institutions very seldom if ever consider the costs, the early formative costs, of doing what you're recommending we do of sitting down, of listening, of doing that fishing expedition so that we are indeed conducting the most relevant of research as we interact multilaterally. And even when within country,

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there's not a clear map of the power structure, so very often you're interacting with other academic who have very similar interests who other western academics [misspelled?] and you're not really identifying the most relevant of research when that is a locus of interaction. It almost takes ideally sitting down with the village people to ask them, "What are the questions you need answered?" but that costs money and time to even come up with the proposal. How do we get around that?

SOLLY BENATAR: Yeah, thanks, Ken, for offering that question. Look, it's a long route. It's not something that's going to be achieved overnight. But let me again tell you that very significant progress has been made, so let me give you an example. The NIH is pumping millions of dollars into HIV vaccine and microbicide research in South Africa, and much of that money is being spent on just these issues, community engagement, debates with the community about the implications of what their studies will mean, educating them about HIV/AIDS and treatment, and the NIH is beginning to understand as the funding body that preliminary work is required before you can undertake that kind of research. So the funding is coming on stream, actually. The kind of funding that the NIH is providing to me as a principle investigator, the totally new series of programs around the

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developing world, is recognition that this work need to be done as preparatory work for good studies to be taking place in the future.

So I think the funding bodies are beginning to understand that, but I think we shouldn't leave it entirely to them. There are other organizations, so I would imagine that, for example, a powerful enough drive by people from the UK working with [inaudible] could accrue some resources to some of those aspects of the program because there are people in other aid programs who could actually be conducting some of that work with us through other sources of funding. So it requires imagination. It requires a vision. It requires a dedication. And it requires not allowing us to say it can't be done. We just have to push our way forward as the treatment action campaign and [inaudible] and other endeavors have in making the kind of progress. So any major problem in the world, be it slavery or [inaudible] toward other kinds of disparities in health that we are facing, will not be easily overcome. It requires a profound battle by many people across many fronts, a great deal of scholarship, a great deal of activism, a great deal of support by philanthropy, and over ten or 15 years I hope that there will be considerable progress. I've certainly seen progress in the last 10 years in just the issues that we're talking about.

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KENT: Hello.

ANNE FANNING: I think in this aisle, and then we'll go to the middle aisle. Thank you.

PROFESSOR MILLER: Thank you very much, Professor Benatar. I think I can promise you that the ethics advisory group of the union, which has recently been set up, and which I think is perhaps its existence is not as well known as we hope it will become. We need all the advice, all the help, and all the insights, which people like you with so much experience can offer us. And we're grateful to you for coming to the workshop we hold on Wednesday morning and Wednesday afternoon and we look forward to continuing to benefit from your wisdom and your insights. And you've provoked us, stimulated, and educated us in most invigorating ways today, and thank you for that.

Could I say one other thing, which is that the Union, of course is involved in certainly research and in trying to promote effective and ethical research, but its brief goes wider, of course. It goes to provision of technical assistance in the development of health services and in the broader education. And I think a great deal of what you had to say to us today could be equally translated into the ethics of the provision of technical assistance, technical advance, and also in the Union's educational activities. And

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I hope that one of the future educational activities may be in assisting and promoting education in the ethics of research and development, as well as of research.

And finally, may I just say to my fellow members of the Union, we in the ethics advisory group, we certainly greatly appreciate your support, your advice, and your input into our activities. We are only newborn, fledgeling, and we have a lot to learn, and we should be grateful for all the advice and assistance we can get.

SOLLY BENATAR: Thanks, Professor Miller. And if I could just make one brief comment in response to that: When you talk about ethics, we tend to talk about ethics at the level of interpersonal relationships, how we should interact with our patients and how we should interact with our colleagues. It's largely interpersonal ethics that we talk about. But you've raised the issue that we've spoke about elsewhere, and that is how the ethics debate needs to extend beyond that. So, for example, how any organization operates, how any hospital operates, it has an ethical basis to it. How are decisions taken? Are institutions accountable? Do they spend the resources that they use, which are often public resources, in a way in which is acceptable to those to whom they're responsible? The ethics in how institutions operate is increasingly becoming under scrutiny. And there's

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a wide-ranging suit of ethical principles that could be applied to those discussions, which could improve the way institutions function because if institutions don't function well, the individuals within those institutions battle to meet their own model requirements because they're left out in the cold.

So for example, in health care institutions, if physicians have to make resource allocation decisions at the bedside, it becomes very difficult. If health care policies are made, if the rationing parties are sorted out at a health policy level and they're accountable and transparent in public, then clinicians can more easily fit in within those constraints which are required for use of public funds in the uppy and beneficial manner. So yes, there's the ethics of institutional arrangements such as the Union and it goes beyond that.

As I suggested earlier on in my talk, every political decision that's taken has an ethical aspect to it, and the ethics of international relationships and how international relationships should be conducted, how business should be transacted at global level is increasingly becoming under ethical scrutiny. Brilliant writings by many philosophers on those issues. Whether their impact on the real world or not

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is another story, but people are certainly thinking about those issues.

MARTIN GRAHAM: Hello. Thank you for your very fantastic talk. My name is Martin Graham from [inaudible] from Malawi. And I want to comment on one specific part you said about a placebo debate, a hotly debate, which was in the year 2000 and before and an example of that how it can backfire to the trials and to the implementation of scientific work. We had that time a [inaudible] trial, placebo-controlled, which because of this debate has to be stopped immediately. We had to wait for one year and then we made a trial of comparative trial and inferior trial of two dosages of cotrimoxazole. I think that just this whole issue of debate then caused the introduction and the scientific [inaudible] cotrimoxazole in HIV positive patients has been delayed by this debate and therefore backfired on the introduction of it and maybe more provocative it was unethical to stop these trials.

SOLLY BENATAR: Yeah. I would suspect you're right because you see unfortunately when they are complicated ethical issues, you can't have cookbook [misspelled?] answers. You can't look at a book and get an answer in the same way as complicated clinical judgments that needs to be taken. They require a broad range of knowledge, the ability

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to morally reason and the relevant aspect out, and as I've said before, I think that the placebo-controlled studies have to be evaluated on their merits. If there are vast advantages and minimal harm shown in the placebo-controlled study, even though that study may not be conducted in the developed world, because the whole balance of harms and benefits would be totally different, that doesn't make them any unethical in developing countries.

It's very hard to get that past people who believe not only in ethical universalism, but ethical absolutism. There are those dogmatists who believe that ethics is absolute dogma. Philosophers will always tell you that every ethical question is never finally resolved. You can always find a deeper and more complex argument to look at something more carefully, which is why philosophers write those long books about exploitation, for example, so I don't want to undermine that kind of debate by some of the comments I've made, but I do think that trials may not be started or may be stopped on grounds that are not well thought-out, so I take your point.

ANNE FANNING: Ladies and gentlemen, I think we have just less than five minutes left, and I'm going to say the three questioners; one, two, and three, in that order will be

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the last, but I'm sure Dr. Benatar would be prepared to stay afterwards. Asmelis [misspelled?] Tony?

ASMELIS TONY: Asmelis Tony from Sudan. I think there is room for partners from [inaudible] countries again to play as far as ethics of [inaudible] concerned and most important not to be passive. And I perhaps think it would make it very difficult for people to [inaudible] whether they're from the west or elsewhere if they don't apply to the norms of our societies. But what do you think if we would like really to come up with solid conclusions about ethics and reaching of ethics in [inaudible] countries and elsewhere to have some sort of a study like conceptual mapping of research partners at [inaudible] countries and the conceptual mapping again of how the subjects themselves think and then we can come up with solid conclusions? Thank you.

SOLLY BENATAR: Yes, I think I've said that in my talk today. I think that we must understand and involve in a dialogue people from other countries, but we mustn't accept that everything that other people do in other countries is right in the same way as we mustn't accept that everything that we do is right. When I have a dialogue with someone from another country I often learn a lot of things about their country that are good that should be done. I often learn a lot of things about their country that are bad and

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that shouldn't be done, and I have to learn to mount the arguments against those two. And I often develop a deeper insight into what's good about what I want to do and about what's bad about what I want to do and I have to be self-critical too.

So the ethics debate must be a critical debate. It must be one in which one can with an open mind examine the ideas and the concepts and the issues that are raised and then try to provide the best justified arguments and have those open so anybody can contest those and look at them. And my suspicion is that if we enter into that debate we'll find a middle ground that doesn't exist at the moment.

ASMELIS TONY: You referred to conceptual mapping of the subjects and the research partners in a discussion group and we did that for people living with HIV, and we were hired by the UN to do that, and they came up with very different views; that the virus is going to eat us, this and that, so conceptual mapping for subjects, as well as for partners from the [inaudible] countries might give you very astonishing results.

SOLLY BENATAR: I understand that, and I'm sure it's too big a subject to pursue today, but we do need to try to be as rational as we can in these issues. We all have elements of irrationality about the way we think, and we do

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have to try to provide justified arguments for things that we're going to do at the public level. What do you believe personally can often be off the wall, but if we want to introduce at the public debate it must be something that the people can link into, so it is a complex issue that you raised. Thank you.

J.J. MCCONNELL: Thank you for the insightful presentation. I'm J.J. McConnell from South Africa. The question I want to ask is usually the power between the researchers and the subjects is really [inaudible], and quite often governments in resources limited settings find themselves in a trapped way [misspelled?] where such activities take place in their own back yard and they have very little control because of local funds and so on. How would you, in your [inaudible] advise, government [misspelled?] in all those areas that they would be able to control and have input into what comes into those countries because often their power is taken away from their hands just from the [inaudible] that they have very limited resources and a lot of unethical researches take place within their own back yards. Thank you.

SOLLY BENATAR: Thank you. That's a very important question and I can just try to answer it very briefly but not comprehensively. I think the way forward is for ministries

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of health in developing countries to try to develop national research ethics committees, not to evaluate protocols but to see the standards for the research ethics in their own country, and this is precisely what's been done with the health act, as you know, in South Africa.

And then there's a requirement within that act that members of research ethics committees should get some education about research ethics and not just be people who come into it without education. And that, of course, is empowering and it enables people to transform the research agenda and to turn away certain research projects and to take on board others. The problem is that the money lies often with people in the pharmaceutical industry who just want to conduct studies in countries that have very little relevance to those countries, and yet that's the only way to get resources into the countries. And that's part of being impoverished and it's part of the system that maintains poverty. If poverty is maintained through all those forces that I've indicated to you before, and if there is no other way out of poverty than to accept something that somebody wants to do against your own wishes in your own country, people will do it. So that's why I painted that broader context.

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At the same time, I was trying to research more ethical and research programs more ethical. We should be fighting at another level to try to emancipate poor countries from the slavery of economic poverty.

MEGAN [misspelled?] MURRAY: Megan Murray from the U.S. I wonder if you think that research journals have a role to play in enforcing or promoting the kinds of research standards that you've talked about today.

SOLLY BENATAR: Sorry, I'm used to wandering around with one of these lapel mics. Yes, I do think so. I think what might be very nice is if every research journal, for example, were to, say, reprint a really excellent article from, say, a research institute journal or from some other journal that makes some very important points that might be relevant to its own research workers, or if it would commission an article around a particular subject, that would be enormously important. So if the *American Journal of Respiratory Critical Care in Medicine* were to carry one article a year on an important ethical topic, that would be of great value, so yes I think that's a wonderful idea. I hadn't thought about it myself before. Thank you.

ANNE FANNING: Ladies and gentlemen, on your behalf, I would like to thank Dr. Benatar for his profound insight into these very challenging issues. I would like to thank

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him for providing a mirror for ourselves. I think he has tweaked our consciences to make sure that our science is relevant and meaningful and partnered. I think that he has challenged us to make sure that we do the right thing and to assure that it - and to encourage us that it may, in fact, be the smart thing. The long-term benefit is that it will yield bilateral returns. And finally, I think he gives us hope that all is not lost, so I thank you.

[Applause, laughter]

[END RECORDING]