



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT
Medical Research - the Global Landscape

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DR. WAGNER:

Thanks, Amy. And thanks so much for that background, Val. We appreciate the report you received.

As our presenter is coming forward, I will remind the Commission and those visiting that this particular topic comes to us owing to alarming reports of history. And I guess one could use the word egregious, particularly in terms of our current standards, the standards of our time. But I think we need to be reminded also that there are good and right and advantageous reasons to be pursuing human subjects research in clinical trials for the benefit of the public for public good and to do those here and abroad when they are done within the contours of ethical practice.

So we are going to hear something about the context and important questions of clinical trials from our two speakers in this first session. Our first will be Dr. Lawrence Corey. He is the President and Director of the Fred Hutchinson Cancer Research Center and Professor of Medicine and Laboratory Medicine at the University of Washington. There he leads the virology division in the Department of Laboratory Medicine. He is an internationally renowned expert in virology, immunology, vaccine development and principle investigator of the HIV vaccine trials network, which is an international collaboration of scientists and institutions dedicated to accelerating the development of HIV vaccines. In recognition of his achievements, Dr. Corey has received the Pan American Society Clinical Virology Award, the American Society for STD Research Parran Award, and the Infectious Diseases Society of America Ender's Award.

Welcome Dr. Corey, we are delighted to have you with us today. We look forward to hearing from you.

DR. COREY:

Thank you Chairman Gutmann and Committee members. It is a pleasure to address you today about the issues of the current and upcoming landscape of medical research in the developing countries. I am going to address these issues from several perspectives.

First, as a life-long physician scientist and viral disease specialist who has been involved in the HIV epidemic since its inception and for the last decade, I have been involved in the global effort to develop an HIV vaccine. And since 1998 I have led the National Institute of Allergy Infectious Disease supported, as you mentioned, HIV Vaccine Trials Network.

The HVTN, as we glibly call it, has been created to speed the development of an HIV vaccine and it coordinates a global clinical trials

program devoted to HIV vaccine research. It operates on four continents in 15 countries and nearly half of its research efforts are conducted in developing world, specifically Sub-Saharan Africa, and its efforts in this part of the world are scheduled to markedly increase.

I am sure all of you are aware that the developing world bears the greatest burden of HIV and hence the development of novel HIV prevention strategies including a vaccine are necessary components of the global medical research agenda. Perhaps it is intuitive that many if not most infectious diseases studied should be studied at the global level. The worldwide transmission pattern of SARS, H1N1 influenza, methicillin-resistant staph aureus and penicillin-resistant streptococci have taught us that we are all increasingly interconnected.

For communicable diseases, a global research platform is both efficient and necessary. To appreciate the contributions of global research, one only needs to pick up last week's New England Journal of Medicine to see an article from the Chinese CDC headed by Dr. Yu Wang which reports on the safety of 90 million Chinese adults and children who received the H1N1 variant influenza vaccine. The article reported no increase in the frequency of Guillain-Barre Syndrome, the side effect seen with a previous swine influenza vaccine in the 1970s in the United States. And the article provides an important piece of information for future vaccine policy in the U.S. and Europe.

I also want to talk about the landscape of global research for chronic disease, especially cancer. On this topic, I speak from my perspective as President of the Fred Hutchinson Cancer Research Center in Seattle, one of the original five National Cancer Institute's designated cancer centers created by President Nixon in the early 1970s. The Hutchinson Center is where bone marrow transplantation was pioneered and is one of the largest free-standing research centers in our nation.

Cancer is the world's leading cause of death. It may come as a surprise that the global burden of cancer in the developing world is even higher than in the developed world, especially for cancers that might be preventable or effectively treated. We need to recognize this global burden of disease and initiate a plan to include cancer prevention screening, and treatment, into the global research agenda.

Now the goal of medical research is to improve health, improve survival, and the quality of life. The attainment of these is a universal desire of human kind. The link between disease burden and economic and social development is clear. Poor health and disease are not only markers of poor economic development but also exude a causal relationship to poverty. Poor health equates the high maternal and infant mortality

rates, poor childhood survival, decreased adult life expectancy, high burden of acute and chronic disease, and increasing poverty.

Importantly, poor health influences access and the ability to take full advantage of schooling. This directly reduces the ability both from an individual and for a country to compete economically. If one is to have a global development strategy, then one needs a global health strategy. And by definition, one needs to have a global medical research strategy. Improving health globally requires improving the research infrastructure locally for those working in health. Thus perhaps the first obvious point for surveying the global landscape on medical research is the critical need to expand the types and the amounts of ethical medical research in the developing world.

Now how do we create the tools and safeguards to implement a global medical research agenda? I will maintain that we already have several successful models. Perhaps the most developed is in the area of HIV prevention and therapy. For the last five to seven years, most of the sentinel advances in HIV treatment and prevention have arisen from studies conducted in the developing world. These studies have been conducted at the highest ethical and investigative standards and are shaping both the research and clinical practice agenda of citizens in both the developing world and industrialized countries. I would like to highlight three successful insights in HIV prevention research that have come largely from trials conducted in the developing world, through successful and ethical collaboration with U.S. and developing world scientists.

The first successful insight for developing an HIV vaccine emanated from a clinical trial performed in Thailand by Dr. Nelson Michael's group in collaboration with the Thai Ministry of Health. This trial has transformed the HIV vaccine research and development landscape.

Most recently the study called the iPrEx demonstrated the concept that is possible to reduce acquisition of HIV by taking antiviral drugs daily. This study has initiated discussion about the use of licensure of such drugs in the United States. Of the 3400 subjects enrolled in this HIV prevention trial in men who have sex with men, only ten percent of the participants were from the United States. Most of the clinical trial participants were from South America.

Another study found that regimens found to be effective in the United States were expanded and adapted to improve the efficacy of regimens to prevent mother to child transmission of HIV in Africa.

And yet another study conducted in South Africa found that starting antiretroviral treatment early in childhood reduced death by two-thirds.

This study has changed international treatment guidelines and improved child health in our own country.

Similarly studies defining when to optimally start HIV therapy and how to minimize clinical failure are all emanating from the large treatment programs initiated in Africa, Haiti, Peru and Brazil. All of these studies have led to improved care for HIV-infected persons in the U.S. and Europe.

Now one of the key features of an HIV research experience is that the studies are relevant to both the sponsors and funders in the developed world, and especially to the participants in the countries in which the studies are being conducted. Conducting effective medical research globally requires establishing mutually beneficial partnerships with local researchers and research institutions. It is critical that local institutions and researchers are involved in conceiving the studies and that input and innovations are valued. It is crucial that the research questions being raised are relevant to the community being studied. In addition, the community must be involved in defining the standard of care for the study. Within the HVTM, we operate on a pretty simple principle. All the research studies, all the research sites in any study are equal. We use the same ethical principles to guide our research regardless of where it is conducted. Our international investigators are involved in all of our protocols, including ones conducted solely in the United States.

International researchers occupy leadership positions in our research network. In addition, we are engaged in building in-country infrastructure in low-resource countries where our research is conducted, including building laboratory infrastructures to ensure that laboratory support of research and the specimens are not simply shipped out for the developed country to use.

Now research partnerships need to be cultivated. My personal experience with such partnerships is that having a free-standing independent medical research university, one that embraces the scientific and ethical principles of medical research and that is independent from the ruling political establishment are critical features for implementing long-range programs for medical research. These institutions are able to provide the human capital and the forms for training the diverse groups needed to perform research, especially those involved in establishing the ethical standards and reviewing research conduct. Cultivating such institutions, engaging in their development should be an important component of the overall strategic plan for biomedical research.

Partnerships also help ensure that the research being conducted will be of benefit to the communities involved in that research. Do we value the

input in innovation of southern hemisphere investigators. Again, the HIV field provides some useful examples.

In Sub-Saharan Africa, three clinical trials in circumcision of heterosexual men were conducted to evaluate whether this procedure would reduce HIV acquisition, a strategy that dramatically and directly reduces a Sub-Saharan African man's HIV risk. Based on these results, South Africa, Swaziland, and a variety of other countries have initiated countrywide programs of adult male circumcision to reduce HIV acquisition. Such an approach for reducing HIV acquisition among certain populations in the U.S. warrants such a discussion. Now involvement of the community, especially the nonscientific community is critical for successful research in the developing world. The community must be involved in the conceptualization of the research itself not just in the IRB and informed consent process.

Our organization has spent both energy and time in developing meaningful community engagement, not only for each clinical trial site, but also for the organization itself. Community members sit on all committees. They have equal voting rights and access to all documents. The HVTM supports the travel of community members to its meetings, where we develop our research protocols in investigator forums. They are as integral to the research process as are the researchers themselves. The guiding philosophy is that a global research network should have fundamental working principles that are applicable for all its components. Cultural and linguistic differences must be acknowledged when communicating medical information, such as the pros and the cons of genetic information.

It is challenging to explain the importance of host genetic susceptibilities to disease, genetic determinants of drug metabolism, or the sequencing of a tumor to provide information on how to optimize therapy. The process of informed consent must also be developed with community input. This Committee needs no discussion from me on this issue. Suffice it to say that true consent goes beyond signing a 12-page document and must incorporate many ways to reach the audience, whether through visual aids, DVDs or street theater. Informed consent is about making sure there is understanding of the research and the research process. It is not only conveying information but also assessing whether someone understands the research study.

We are quite an individualistic culture, one that values autonomy and believes in the concept of individual privacy when making an informed consent decision. Yet in some cultures, community assent is critical, if not essential for participation.

Another important component to the global landscape is equal access to therapy within the context of the trial. Are there differences in standards of care between sites involved in the same research study? While this is an issue that may vary between trials and locales, this is an issue that must be worked out among all the research partners.

In the HIV prevention field, we needed to deal with access to antiretrovirals among persons who acquired HIV on our trials. HIV is not a complication to the trial but often an inevitable outcome of living in a country with a high incidence of HIV. We needed to examine whether antiretroviral therapy be available for all participants in Haiti as it were for persons in the U.S. To achieve this in many countries, we needed to provide a mechanism to make these life prolonging drugs available to trial participants.

The issue forced me as an investigator at the Hutchinson Center and as the organization coordinating the research to start a nonprofit entity and raise funds for this endeavor. We used these funds to bridge access to antiretroviral therapy until the PEPFAR or global programs could be initiated.

What is critical and yet may not reach the attention of the research establishment is the need to provide the personnel funds and funds to engage local communities and problem solving on the types of issues I have raised. I would urge the Commission to encourage that such funding be made routinely available, particularly for trials sponsored by private enterprises and foundations.

The commitment to action following the research is an area of most concern to me, as one expands the global research agenda. Here is where the global burden of cancer may be used as a model. Now the statistics on the global burden of cancer are staggering. In 2008, 12.7 million cancer deaths, 7.6 million cancer deaths are estimated to have occurred worldwide. Of these, 50 percent of the cases and 64 percent of the deaths occurred in the economically developing world. Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer deaths among women, accounting for the 23 percent of the total cancer cases and 14 percent of the deaths. Lung cancer is the leading cancer site in males, accounting for 17 percent of the new cancer cases and 23 percent of total cancer deaths. And breast and cervical cancer are now the leading cause of cancer death among females in low resource settings. Cancer survival tends to be poorer in developing countries, most likely because of a combination of late stage of diagnosis and limited access to timely, and for industrial countries standard, treatment.

In Uganda, we see mortality rates above 50 percent for children with Burkitt's lymphoma, a cancer with proven curative therapy. The rate is high because of lack of access to treatment.

A substantial portion of the worldwide burden of cancer could be prevented through the application of existing cancer control knowledge and by implementing programs for tobacco control and vaccination for liver and cervical cancers in particular.

We at the Hutchinson Center and I, personally, am committed toward developing and extending cancer research programs into the developing world. We are currently involved with building and staffing a new outpatient research and training cancer center in partnership with the Uganda Cancer Institute and the Uganda Ministry of Health in Kampala. In addition, we have initiated a training program for Ugandan physicians in medical oncology.

When we started, Uganda, a country with a population of Texas had only one medical oncologist and we have trained four and have three more in our current program. With help from the Fogarty and recent study from the National Cancer Institute, and in partnership with Makerere University in Kampala, who have now extended our training program to a wider scope of health professionals and administrative personnel required to perform a long range research program in both HIV and non-HIV related malignancies. We view this program as potentially transformative with respect to breeding novel therapies, including novel cost-effective regimens to medical oncology.

Although there are many details to such a program, the one that I would like to highlight what I think will be a common ground for discussion for the global research agenda for cancer and chronic disease will be access to successful novel therapies, especially in novel therapeutic that has extensive development costs.

Now access to successful new therapies must be discussed at the time the research experience is initiated. While all aspects of such discussion need not to be solved prior to the conduct of research, some common understandings must be acknowledged and their principles articulated on paper. There are models for this issue. Many global foundations, especially the Bill and Melinda Gates Foundation, have pioneered such discussions. They require global access agreements for all the research they fund.

No such agreements are required by the U.S. government standards or through commercially sponsored agreements. Realistically, these agreements are complex, involving the sponsors, the investigators, communities, health ministries, and local regulatory agencies, —

DR. WAGNER:

Dr. Corey, this is wonderfully fascinating. I need to move you along.

DR. COREY:

I have got two minutes.

DR. WAGNER:

Perfect.

DR. COREY:

All right.

— a task that is daunting and often foreign to the investigators posing the clinical trial.

It is unlikely one set of standards can be developed for every type of innovation and graded uptake of a novel therapy may be acceptable in many instances. At a minimum, acknowledgment of the issue and providing the administrative framework for initiating these discussions should be in place.

In summary, new investigative areas will expand, especially in chronic diseases that burden both the developed and the developing world. The increasing morbidity of diseases such as cancer and diabetes and heart disease will require the establishment of new global research networks and collaborations. Successful models of international collaboration do exist. They are based upon mutual beneficial long-term partnerships, partnerships that involve funders, investigators in both the developed and the developing world, and study participants with meaningful community engagement. These collaborations are, in my opinion, scalable.

The most successful clinical trials are those that are conducted expediently yet prudently to ensure the research is carried out at the highest standards and protects study participants from harm. Governments, especially the United States Government, which has led the world in global research partnerships, must drive this process. So thank you for the opportunity to address the Commission and —

DR. WAGNER:

Dr. Corey, thank you. We are going to move to a colleague before we go to questions. Val, I assume, Dr. Corey permitting it, we can have copies of that statement.

DR. COREY:

Yes.

DR. WAGNER:

That would be wonderful.

All right our next speaker is Professor Robert Califf, Vice Chancellor for Clinical Research and Professor of Medicine in the Division of Cardiology at Duke University Medical Center, the leader of many landmark clinical trials in cardiovascular disease. Dr. Califf remains actively involved in the design and execution of multi-national clinical trials. He is currently the Director of the Duke Translational Medicine Institute, which is an organization focused on how scientific discoveries are translated into improved medical care.

Dr. Califf has served on the FDA's Cardiorenal Advisory Panel and the Pharmaceutical Roundtable of the Institute of Medicine. He is a member of the IOM Forum on Drug Discovery, Development, and Translation, also serves as co-chair of the Clinical Trials Transformation Initiative. Ron, thank you for joining us today.

DR. CALIFF:

Thanks.

DR. WAGNER:

Great to have you here.

DR. CALIFF:

Great to be here and I want to thank Dr. Corey for an elegant discussion. I am going to take a little more of a down home approach here. I am going to show some slides. And I know I need to move quickly to get this done in 15 minutes or 14 point something.

This is such a complex topic, all I can hope to do is to introduce you to some of the things that happened in real life as we deal with this multinational clinical trials environment that we are in.

So first just my disclosures, which I am used to giving. I obviously do have a bit of a conflict of interest. I do this for a living. It is a passion for me. And I also should acknowledge that part of what I will have to say today and a great learning experience for me comes from the fact that we have a Duke Medical School in Singapore now. So when I present, I can present as an American from an American medical school or I can present as an Asian from an Asian Medical School. And the context, as I will show you, could be quite different particularly at the end.

So, this was the assignment that I got in writing a couple of weeks ago when I got the call. Describe the contours; discuss the benefits of international medical research; and review issues in need of attention. And I will try to cover all three quickly.

I will refer you to several pieces of work that we have done. Probably the one I am the most proud of is a paper that was first authored by Seth Glickman, who was an emergency department physician at Duke and initially entitled this “Clinical Research not made in the United States.” The New England Journal forced us to change the title to the one that you see here to be more politically correct. I still think Seth’s title was actually more appropriate.

The point here is that we are seeing a massive shift in the conduct of research. It used to be dominated by the United States and, as I will discuss, many people are now asking is the United States even a fit place to do clinical research in the international context.

I am not going to go through this in detail but if you have a chance to look at the article, we go into a lot of detail about the issues. We don’t have answers to any of these questions. So I think the timing of your involvement in this Commission couldn’t be better because we are in the midst of massive global change in this endeavor.

Now if you ask why is this happening, to a large extent, what we are seeing is a large shift in economics and finance occurring at a setting at which the marketing of medical products has become global in every respect. And if we think about the way patent laws work as we are now exporting our view of patent law to the rest of the world highly effectively in places like India now, for a company that is developing a medical product, the time from getting the patent to launching the product is really the critical issue.

And if we think about return on investment for industry-funded research or if you took a public health perspective globally and you said getting an answer for global populations is a critical issue, the maximum return on investment is going to come from obviously getting the research done more quickly by involving more places who can enroll research participants in the clinical trials and get those answers so that future participants will know — so that future patients will know they are getting the right treatments based on evidence, instead of someone’s expert opinion. The old day of the doctor having the expert opinion and being correct is long past conceptually but I don’t think our cultural expectations in terms of the distinction between research and practice have made up for that.

Now just to make sure everybody is awake, I have taken three newspaper clippings from a place where we are doing a lot of research and I am spending a lot of time now in India. A place where by the way when we call India a developing country, the most common retort I get from that is wait a minute, we were developed before you existed. And if you want

to look at developing, go to Washington, D.C., where some of the disease rates for infectious diseases are higher than almost anywhere in the world. You had better look at your own country in terms of what is developing and what is not. And yet, there are issues that need to be addressed as evidenced by this series of articles that came about in the Indian press.

And by the way, many of us get frustrated with the American press these days. The Indian press is really something to behold when you are working in India.

Now, the business case here couldn't have been put better than by J.P. Garnier who was the head of research at GlaxoSmithKline not too long ago. And this pretty much tells the story. If you can move 50 percent of your trials from high cost places such as U.S. and Western Europe to low cost places such as India and South America, a mid-sized pharmaceutical firm with 60,000 patients in clinical trials could save 600 million dollars a year. This is simply a fact. And pretending it was different is not going to change that fact.

And then we have to face the issue that we now know for the United States if our people are going to get the right treatments, we have to do more clinical trials probably by a log order with a least a log order more research participants to get the answers that are relevant to our own country. So how do we deal with all of this?

So first of all let me just make the point that when it comes to doing clinical research of any type, it is done in the context of a research site, which has been alluded to already. A site has to include an investigator, a study staff, an IRB or some ethics component, and a business component because all of this costs money and takes time that has to be accounted for and dealt with. So when I think about this, I divide it into several basic types of coordinating activities, and you will see why this may be important in a minute.

Site-based research, which is actually putting your hands on research participants in dealing with them, Type 1 is research that occurs outside of a patient care arena. It is very different. You can enroll people in a study, treat it purely as a study. You are not mixed up with clinical care. Type two, which is the type that I do, involves clinical care as a mandate because you are dealing with sick people who are getting other medical care and they are also participating in a clinical trial. And then of course, you have community-based and field research, which is different than anything involving the typical medical care setting.

So I am going to give you some very gross generalizations now. I am going to fly through this. The slides will be available later. And I want to make some just key points.

First, all countries need clinical research done in their populations in the context of their healthcare delivery systems. That is, I think, something we are all coming to realize now.

Second, almost all countries have a mix of excellent, highly appropriate research sites for human studies, poorly managed sites, and outright inappropriate sites. And that is true in the United States as well as every other place in the world.

But in common discussions, as I am involved in almost every day where we are going to a global clinical trial on a chronic disease and we ask the question what are we going to do to get the research sites to participate in this trial, what we commonly hear is that North American and Western Europe are expensive, bureaucratic, and inefficient with an overly inflated view of their own quality. South American, Eastern Europe, and Asia are much less expensive with mixed quality and many excellent research sites. Africa and the Middle East are emerging. I am going to just quickly go through each one, just to make this point again. Again, not to give you anything definitive but these are just things that people say.

North America. We are really great at coordinating studies and telling other people how to do things, particularly in research. We have well organized non-clinical site-based research. What I mean by that is we have professional research centers in the United States and Canada that do quite well with volunteers in studies that don't involve critical illness. But our site-based research in the context of medical care is poorly organized and relatively poor quality compared to most of the rest of the world, at this point, mostly reflecting our fragmented healthcare system. Our field-based research is extraordinarily expensive compared to anywhere else in the world and very highly inefficient. And most of the rest of the world looks at what we do and says: why would we want to do things the way that you do it? It is not very good for getting answers for our people.

South America. Low cost, large enrollment capability and a mix of very good and very bad research without much organization of field-based research.

Western Europe. Very expensive, bureaucratic, excellent at coordinating but much better organized for research done in the context of clinical care because they have healthcare systems that are organized where you can collect data in an organized way.

Their field-based research is outstanding because many of the countries have national patient indexes with numbers for everyone so they can be followed without the tremendous expense and disorganization that we have in the U.S.

Eastern Europe. Low-cost, highly organized, very high quality data in many sites and then some mixture of some bad research, too.

India, China, the ASEAN nations. The 900 million people who live in the rim right below India and China, remember over 3.5 billion people have poor academic infrastructure, poor coordinating capabilities at this point, and mixed clinical site-based research. There are a growing number of excellent hospitals and practices who can do chronic disease research with the same quality or better than we do in the United States. And then Africa. Low-cost and evolving in very different kinds of research being done there that I think we are just learning how to do. But I would also point out that Africa is also seeing this emergence of chronic diseases such as vascular disease as a major cause of death that we will need to learn to deal with.

And then the topic of the day in globalization, the Middle East. Except for Israel, the Middle East has mostly been left out of global clinical trials. But due to the rapid advance of information technology, which is having other effects that we are all talking about this month, there is a lot of discussion going on right now about much broader involvement in the Middle East. The epidemic of diabetes and vascular disease in the Middle East makes the U.S. look weak in terms of the amount of disease. So, then just a few more things. International variation can be due to genetic variation, concomitant therapy, medical practice variation, or cultural perceptions of random variation.

I just want to make the point that there is variation and outcomes everywhere in response to treatment. This is a map of the U.S. for vascular disease. Not good to live in the Mississippi Delta if you want to avoid vascular disease. In our own county though of Durham County, North Carolina, we see the same kind of variation, depending on what zip code you live in. And we are now taking this to the neighborhood level. There are radical differences in your risk of succumbing to a disease depending on what neighborhood you live in the U.S. This is a global phenomenon that I think requires that we do studies that involve every country and every culture.

But in addition to that, the results of trials in the U.S., at least in vascular disease are different than the rest of the world. This is the FDA's data not yet published put together by Bob O'Neill who heads up the major statistical effort at the FDA looking at 16 independent major cardiovascular trials that were global in nature and the fact is that the

treatment effect observed in the U.S. is less than the rest of the world, highly statistically significant.

This slide, I had one of my Scandinavian collaborators to actually debate with me at the Heart Failure Society of North America where he took the position that the United States should be excluded from participation in Phase III clinical trials because we never see a significant result, mostly because we have a very high dropout rate from trials and we don't collect very good data. So his view was, we should be excluded because we are a low quality place to do clinical research.

Genetics are also important and this is from a study by David Goldstein and John McHutchinson just happens to be one of our local studies, but there are many others coming down the pike. I don't have time to go into the details but you all know hepatitis C is a global epidemic, interferon is a nasty treatment but also effective in some people.

It turns out that the genetic of handling of interferon have now been at least partially worked out and we had observed for a long time this variation where Asian people respond much better to interferon than African Americans in particular and Caucasians are in-between. What we discovered was that if you know the genetic polymorphisms, the effect of race is no longer important in the response to interferon and I am going to skip through the details of this quickly and just make the point that if the trials had only been done in Beijing, it would look like interferon was God's gift to mankind. If the trials had only been done in downtown Atlanta or Durham, it would have looked like a terrible treatment. And so only by doing global studies have we discovered this. And then finally, the importance of cultural variation in my own field. There are treatments that are effective in one cultural context that are entirely ineffective in another because the other treatments that people get are very important and the way that the culture adapts to the treatment, even including non-medical elements, such as herbal treatments, can turn out to be critically important. For example in Korea, the diet makes the administration of warfarin very complicated and difficult, compared to any place in the world.

And then just to give you one hot example that is currently in play in a trial that we coordinated together with European colleagues but it was global in nature, clopidogrel, a highly effective now generic drug for vascular disease was taken up with a comparator called ticagrelor, a brand new drug developed by AstraZeneca.

DR. WAGNER:

You've got about a half a minute, Rob.

DR. CALIFF:

Got it.

We did a global clinical trial. There was a highly effective reduction in total mortality with clopidogrel. Low and behold, when we looked at 45 subgroups in the trial, the only one that was not consistent with the rest was that in North America the treatment went in the opposite direction. This had led to not approval yet by the FDA. None of us know the reason. It may be what the Oxford Group showed, which is that even if you look at astrological science you see variation.

And then finally, I want to show this, I am going to get to the bottom line on this slide, rather than go through this, you will see when the slides are made available. I want to introduce this concept of cultural arbitrage. And this is the view that if we regard clinical research as a social evil that people have to be completely protected from and other societies view it as a social good, the research will move to those other societies. This is a point made to us in Singapore by the Singaporeans as an international strategy to move research out of the United States.

So in conclusion, I say all this not because I know the answer. I think we are in a global world. We all have to consider each other's values. The United States can't tell other people what to do. We need to work together as I hope your Commission will do to reach a common ground across all countries about how research should be done.

DR. WAGNER:

Thank you. In fact, thank you both very much.

[Audience Applause]

DR. WAGNER:

We are in good shape for several questions. I just want to make sure — I have been trying to collect some of the thoughts that counter the skeptics that say really part of the biggest motivation to do international trials for American Institutions to do international trials is the expense. I think you have catalogued a pretty good list, both of you, the notion that we need to be other places because there are local health care needs and the variabilities you point out. The fact that global health is local health, I think is one of the points you were trying to make, that cancer and vascular disease is not limited by political boundary.

An interesting one was on differences in healthcare delivery systems. And I believe, Rob, that was you making that comment but I didn't hear you elaborate on that. So I was curious about that particular aspect.

DR. CALIFF:

The easy case to make is in the case of devices, which are increasingly important for chronic disease treatment. It is obvious that if you are in a place that has a high-tech environment where there is excellence in delivery of the device into the person that the device may be highly beneficial. But if you are in a place which is not very good at delivering the device, it could actually be detrimental.

But in the same way there are interactions among drugs and interactions among drugs that are taken with herbal treatments and other aspects of the delivery system. You just can't extrapolate the results from one place to another without understanding that.

DR. WAGNER:

Questions from the Commission? Let's start with John, Christine, and Nelson, and Dan.

DR. ARRAS:

Thank you for two excellent presentations. I would like to get your views on the question of how research projects are conceived. Okay? So I mean the standard norms in the global documents say that research should be responsive to local conditions. Okay? So but there is an ambiguity there. You could be responsive to global conditions in terms of addressing medical conditions on the ground or you can be responsive in terms of the health priorities of the public health, you know, workers in the country or the government or the people.

So how is this conceived of in your organizations? How are the norms of not so much how trials are conducted but like what research gets done.

Okay? Because my sense is that a lot of the agenda is set by organizations in the developed world and sort of gently imposed on these countries. But you have talked about the need for local participation. How does this really work? Is this an ideal that you are giving us or is this a reality?

DR. COREY:

Well it is a reality in some situations. It is a reality in situations in which large collaborative networks have been funded mainly by the National Institute of Health in which the mandate to that large collaborate network is to sort of solve the disease process or problem. And in that situation and that certainly has been an area in the HIV field as a model and that is what I was trying to say, in that model which I think can be easily extended to cancer and vascular disease and diabetes, large multinational problems. If you establish that kind of comprehensive network, especially through U.S. government funding, you are able to essentially put everybody on equal access and equal levels and I think that is what has been done. And so what gets studied is not just what the

sponsor wants but it gets studied by what the medical researchers and the community deem and get prioritized.

I think implicit in your point is that let's say for a pharmaceutical device, they have something that they want done. Now, that doesn't mean it is unethical in any way shape or form but it is to some extent controlled much more by what the desire is.

And then the issue is, how do you get that more in, I guess a favorite word, equipoise. You know, how do you make sure that that is tweaked in a way that is in concert with community values. Sometimes they will truly coincide. If they don't coincide, then I think that is really an issue. How do you define that? And you hope that communities and IRBs and other kinds of issues, and of course, I brought up a major issue that I think is for expensive therapies and for expensive devices is going to be access.

DR. WAGNER:

Of course, all that presupposes a certain level of community sophistication around these issues. Christine.

DR. GRADY:

Thank you both for a very good talk. I wanted to ask as you know a lot of the way we have thought about the ethics of clinical research is by distinguishing it from the ethics of clinical care. And as I hear both of you talk, in the international context maybe more visibly than the domestic context, those lines seem fuzzy. And it sounds like also that a number of the ethical issues that we have talked about access to care afterward, standard of care during, you know, sort of lie at the intersection of those two things clinical care and clinical research. And it was interesting also to hear you say that the efficiency of doing trials is also affected by care.

So do you think it is time for us to start thinking about how we think of the distinction between clinical research and clinical care from an ethical perspective or is that sort of too big of a leap?

DR. CALIFF:

I will speak out on that because it is one of my main things. I think it is past time. And if you look at the construct of the learning health system that the Institute of Medicine has very rationally thought out, I mean, I think a lot of this arose from a time when we believed that there were wise doctors who knew pretty much what to do. And then every once in a while you participate in a human experiment to get an answer as if you were in a laboratory.

What we now know is that medical knowledge is always evolving. We experts often draw the wrong conclusion. And it is only doing randomized clinical trial or another good study that we really get the answer and it needs to be a continuous learning process involving the healthcare system itself, not some separate thing that is kept off in a different place.

Now you know, how to bring these elements together is a very interesting and difficult question but I hope you will address it.

DR. WAGNER:

Nelson.

DR. MICHAEL:

So I would like to understand both of your views on something that Dr. Corey first highlighted, which was you need equal access for research participants or for those who might be research participants in good care. We just spent a lot of time yesterday talking about incidental findings of newer technologies like neuroimaging and genetic studies. And so the walls between care and research I think clearly there is a lot to the discussion that would endorse what you just said.

But I do have concerns. And the concerns are, you know, large networks like the HVTN, my own network and I, Abbey and others I think have done a great job in HIV/AIDS to do just what Larry said. But you know, in the second integration of PEPFAR, at least the U.S. bilateral program for care and treatment delivery for a single disease HIV/AIDS, my own crystal ball shows some degree of lagging support, as those programs go forward. And I wonder if what really you describe I think is the exemplar of being able to have long-term partnerships to build between U.S. and overseas academic organizations, to build all the community engagement in is expensive.

How can we do that in an era where funding becomes constricted, when we are beginning to try to spread this wonderful model to other diseases like malaria, cardiovascular diseases or cancer, how can that be done in the current financial climate?

DR. COREY:

Well I guess I would say I think it is going to have to be done. You know I think HIV created an interesting model with respect to the pharmaceutical industry with respect to the concepts of tiered pricing. You know, that it is acknowledged beforehand that you are going to do tiered pricing and the drugs are very different priced in resource poor countries versus what we pay in the United States. And so that has to be discussed up front and accessed because I think it is just not, you know,

to do a trial in a country and then not make that available either to the participants or the community, you know, I think is quite problematic. And so if you are going to go in there, you are going to have to at least have some discussions. It may be uptake. You know, I think the ministries, the healthcare delivery systems, I think this is what Rob said, the gradation between care and research. I mean, why do the research if you are not going to affect the care? You know, that is what this is all about. That is the necessity of this.

I think our main point is that global medical research is here and if it is going to expand, it is going to expand in chronic disease and we actually need to recognize that and create the infrastructure and the organizational realities to make that happen. And it is going to occur in diseases that have not yet really entered — It is not just HIV or infectious disease. It is going to be in chronic disease.

So we are going to have to create the administrative kinds of dialogues to make that happen.

DR. CALIFF:

I would just add two quick things to that. Number one, we need to ask other people what they think about this because they are dealing with a tradeoff between participation and trials which improves their medical care in general in a country by involving their medical establishment and our rigid view of access. And they often point out by the way, there are a lot of people in the U.S. that don't have access to things, too.

And then secondly, we have to also hold other countries accountable. The finances have shifted. There are 400 million people in India now that are middle class or above by U.S. standards. And so in this discussion, there has to be some demand for accountability by countries that are not so poor as they were in terms of total wealth. It is a shifting environment.

DR. WAGNER:

I would suggest this goes back to your issue about established healthcare delivery systems as well.

Dan it is your turn. As he is a speaker and as that sentence wraps up, if folks in the — or as that answer wraps up, if folks in the audience have questions, they can queue up at microphone. But Dan, your question now.

DR. SULMASY:

I was wondering if you might help me with some basic sort of fundamental disquiet that I have with a lot of the sort of outsourcing of

drug testing. And it is primarily, I guess for Dr. Califf but if Dr. Corey has answers, too, I think some of it is relevant.

You know, when my shirt gets made by poor people in some developing country, I actually feel sort of bad about that, the fact they can't afford it. If the drug, if the FDA were to allow the drug that I take to be manufactured by people who are being paid a very low wage and I get to have it at a cheaper price because of that, I probably also would feel bad about it. But you know, I would wind up doing it.

I feel, I have to tell you, a lot worse though when the drug that I am using was tested on people who are quite poor, will never get a chance to benefit from it. This goes to some of what you were suggesting. And maybe this intuition — And I feel a lot worse about that. I feel a lot worse about it. And maybe the source of that intuition is totally irrational and I suspect economists would tell me that but maybe it goes to the heart of a distinction that I would draw, at least, between products and persons. And then the question is raised of whether at least some of the inefficiency in this country is due, is maybe the ethical price we have for paying some attention to this distinction between products and persons. Tough question but I wonder what your reaction is.

DR. CALIFF:

This is probably the most interesting question that I deal with every day now in what we do. And I am afraid that my view of it is that both are true.

What I mean by that is we are driving research out of the U.S. because I think we have gone too far in terms of rules and regulations which have never been shown to have a benefit. We just keep adding rules and regulations, hoping that is going to fix a problem. And the cost of that is financial arbitrage, which means every time we add a new person that has to oversee something, the cost of doing that in the other country is going to be a fourth or a third of what it is here.

On the other hand, globalization because people need to understand how to use drugs, devices, and therapeutic approaches in their own countries is a really good thing and I think when you deal with people in countries like India and China in particular, most people who are being enrolled in clinical trials are not impoverished people. They are people like you and me who participate in clinical trials because they have chronic diseases and they want to have the right treatment.

So my main point of all this is there is probably a balance between those two that reaches an equilibrium which is more favorable globally than the current U.S. approach or the egregious cases of poor people being enrolled in clinical trials.

To the extent that impoverished people that can't give consent are enrolled in clinical trials, I certainly agree that is a bad thing but it may be less than you think.

DR. WAGNER:

Yes, if you would tell us who you are.

MS. GAPINSKI:

Yes, okay. Rose from Madison, Wisconsin.

DR. WAGNER:

Thank you, Rose.

MS. GAPINSKI:

You just started dabbling and talking a little bit about human subject protocol doing your questions here but the second speaker talked about international research features, which countries are somewhat facilities and our procedures for research which may be good and which are even better. The first person talked a little bit about vaccines, a little bit about a global research agenda and cancer center.

And I am just wondering because the topic today is supposed to be human subjects protection and so far, I mean, that has not been talked about.

DR. GUTMANN:

Can I phrase your question to both Dr. Corey and Dr. Califf? What are the standards that you see as essential for human subjects protection as to make a site, to make a clinical trial valid? Is that fair?

MS. GAPINSKI:

Yes, or why hasn't it been talked about in any — deeply.

DR. GUTMANN:

We want them to talk about it.

MS. GAPINSKI:

Yes.

DR. GUTMANN:

So let's ask them to talk about it. Okay?

DR. CALIFF:

I mean our assignment I thought was to give the landscape and that is what we focused on. But certainly, I mean one of my main points in my

last two slides which I didn't get to, I apologize for that but they will be available, did deal a bit with this issue.

To do clinical research, you need a research site. The research site must have ethics oversight of some kind. And I think this is highly variable in the U.S. and it is also highly variable elsewhere.

This will take about 20 seconds. I want to go through it because I think it relates to several other questions that were raised. If you think about a global clinical trial, you are asking a primary question that may involve a thousand research centers and up to 50,000 research participants. And yet you have got heterogeneity and how that is viewed. So constructing a clinical trial is really a massive social engagement where everyone has to give a bit on what they believe would be the best way to do it. Everyone involved has to give.

And we are learning how to do this better. Social media are becoming important in this. And right now I think we need to evolve to a system where there is less individual variation in ethics oversight and more standardization through the use of social media to involve people at multiple centers in participating in the discussion. I will sort of leave it at that but I think we will get into this later.

DR. COREY:

Well, the Committee was given some excellent handouts by Dr. Grady on the background of the conduct of ethical trials. So I mean, I think our job was to review the landscape, as Rob said.

But I think I did talk about what is the risk benefit and the fact that the risk benefit has to be pertinent to the communities. That you did have to deal with the issue of standard of care. That there are approved IRBs that have gone through the regulatory agencies that certify IRBs. That informed consent is just not signing a document, that it is actually assessing the understanding of both the research process and the research understanding and that there is transparency and involvement at all levels.

So I mean, I think in essence I think the topic sentences I think I tried to cover it in a manner that would be complementary to the handout that was given.

DR. WAGNER:

I think we will ask the final question from our chair. And then actually we will let the audience have the final question. I want to remind the audience that we do have a session late morning. I guess technically it is early afternoon. I devoted it entirely to questions from you. But please stand by.

DR. GUTMANN:

Yes. So I think Rob you mentioned that there is a spectrum from optimal sites to, and I think these were your words, outright inappropriate sites for clinical research, clinical trials. Let's focus on clinical trials.

If we did a random audit of international trials, what would your sense be, given what you know, and I ask this to both you and Larry, of how, what proportion of optimal sites versus downright inappropriate sites — and when I say sites, I think when you said you meant the whole — whether you could conduct effective ethical research under the circumstances in which it has been, it is being conducted?

So what would you say — And let me just say why I ask the question. I think when, this is evidence-based what I think, that when there is a downright inappropriate clinical trial conducted for whatever reasons, it has an effect that goes beyond the way the horrific way, let's say the subjects were treated. It pollutes the atmosphere for medical research and in a way that goes even beyond the horrors of the case.

So I am just interested in whether you think downright inappropriate sites are how close to zero are they? They clearly aren't zero.

DR. CALIFF:

I mean, there are dishonest people everywhere. And I mean what I will say is we do global clinical trials at up to a thousand sites per trial. Almost every one we have to disqualify at least one site for very bad behavior, I will just call it.

And so I would say on a spectrum, that kind of egregious thing is less than one percent. But there is a clear gradation where the most common thing is where the payments for the site for the research far exceed the cultural norm for the conduct of that professional activity of treating a patient with a disease. That is where you begin to get into the trouble, which is not lying but it may be participating in a study which is not optimal for the cultural norms of that neighborhood or environment. And that is probably where the focus ought to be.

DR. GUTMANN:

Okay, very helpful.

DR. WAGNER:

Did we lose our audience speaker? I was looking down taking notes and — Oh, no. Here she is.

DR. GUTMANN:

Larry, would you offer your best judgment on this.

DR. COREY:

I think site development is really an important part of any clinical trial's apparatus. And I think that we have spent a lot of time, often years or two years and hundreds of thousands of dollars to get the site where it is at the normative standards that we need it to be.

DR. GUTMANN:

Yes.

DR. COREY:

And I think that is really one of the interesting issues. I think one of the real issues is where is the constriction point. I mean, to some extent, improving the regulatory agencies and improving the IRB processes, that to which everything needs to funnel, is one area, you know, where I think there needs to be — they define where the centralized point of clinical research will be in a locale and in a country and making sure that the infrastructure of that is at international standards. I think that is really, you know, an important issue.

DR. WAGNER:

And our final question this morning for this session.

MS. BLACK:

Dr. Corey just addressed my question as I was coming to the mike. However, I would like to go ahead and pose it because it is very important to me.

DR. WAGNER:

And your name? I'm sorry.

MS. BLACK:

My name is Millicent. I am from Tennessee.

What weight is given to the requirements for the IRB paperwork for private research institutions on both subjects in the United States and abroad? And more importantly, how are these policies reinforced?

DR. WAGNER:

I think you are right. I think you had touched on that once.

DR. COREY:

I mean obviously, you know, the regulatory agencies within the country and you know, like in Africa, there is a lot of deferral at times to the South Africa. You know, there are stronger ones and less strong ones. And there needs to be a raising of the water level and I think some concentration at a government level at an FDA to international level really needs to be done. You know, that will help all clinical research if

we actually get Europeans, the European Unions and sometimes we actually feel it would be nice to have a European unit of the FDA get together also, you know, to get a little bit more of an international standard at that level.

And of course, you know, for NIH funded research we have requirements for IRBs. And you know, again, local IRBs need to be raised to those levels.

DR. CALIFF:

If I could reinforce just briefly a point that Larry made earlier that I think is really critical, there is a heavy emphasis on paperwork which was the word that I understand the question the way it was asked, but that is not the key thing. You have got to have the paperwork. I am not opposed to having a reasonable amount of paperwork. The really key thing is do you build a culture and a fabric of investigators who, for lack of a better word, who talk back when things don't look right, where there is active oversight of the research by the institutions that are involved, as opposed to simply making the paperwork look good, which I think is becoming a problem at this point.

DR. WAGNER:

We have —

MS. BLACK:

Could I just add one other thing? I'm sorry.

DR. WAGNER:

Very quickly.

MS. BLACK:

Okay. I am aware that particularly research projects in Africa is usually not — it is not unusual for it to be done without the paperwork being in place. And sometimes missions that are called humanitarian is really unethical research being done on African people, children in particular.

DR. WAGNER:

Thank you for that comment.

We have time for only the briefest of breaks, about five minutes. But first let's thank Doctors Califf and Corey.

DR. GUTMANN:

Thank you very much.

[Audience Applause]

