



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT
Social Justice and Ethics Issues

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Meeting 4, Session 8

March 1, 2011

Washington, D.C.

DR. WAGNER:

Okay. Good morning, everyone. Welcome back to this session. Let me announce for those in the audience that we have set aside 45 minutes or so for comment, beginning at 12:35. So what we will do is go through this panel and then we will have a roundtable discussion without audience input. Okay? But please do write down or remember your questions for that session that will begin at 12:35 where we will focus on audience interest.

We are going to talk more about clinical trials around the world. And we have three guests impaneled this morning to speak with us. The first is Susan Lederer. She is the chair of the Department of Medical History and Bioethics and is the Robert Turell Professor of the History of Medicine and Bioethics at the University of Wisconsin School of Medicine and Public Health. She is a former member of the Advisory Committee on Human Radiation Experiments and she has also served on presidential commissions for the German government, charged with exploring the conduct of human experimentation during a period of national socialism.

Susan, welcome. We are pleased to have you here and look forward to your presentation.

DR. LEDERER:

Well thank you and thanks to Valerie Bonham for the invitation to speak to you about the historical development of clinical trials. It should not surprise any of you when I suggest that a historical perspective offers a great deal to evaluations and determinations of ethical conduct and of bioethics in general and not just because I am an historian, but because concerns about ethics and ethical problems do not occur in a vacuum but rather in a context that is shaped by historical contingencies, actors, and events.

And my remarks this morning do not focus on the Guatemala syphilis study conducted by the PHS personnel in the 1940s but more broadly on the climate of medical research and considerations about the appropriate use of human subjects in late 19th century — late nineteenth and twentieth century America.

So clinical trials became the gold standard for evaluating clinical efficacy in the twentieth century. But the word I want to stress there is became. That is, the development of the clinical trial methodology was a process that did not develop linearly over the twentieth century. Initially clinical trial meant simply trying a drug or a therapeutic intervention in the clinic and the medical literature in the first part of the twentieth century is filled with descriptions of efforts, medical efforts to treat say tuberculosis or measles or whatever with a particular preparation but

there is no standardization or attempt to classify and sort out these things.

The process whereby such observations about patient responses to therapeutic interventions came to be re-inscribed, I would suggest, as reliable, generalizable knowledge about the therapeutic practice entailed diverse and multifaceted changes in the social organization of clinical trials about which we just heard. And I would emphasize that social organization is critical, the reconceptualization of the role of researcher and observer, bias understanding of the role of control groups, randomization, and also ethical practices.

Now one pioneering venture in organized and systematic research in the U.S. was the cooperative clinical group study of syphilis treatment. And it perhaps is worth saying, syphilology was a major discipline in itself in the twentieth century and occupied scores, if not hundreds of researchers.

Now this group was organized in 1928 by a small but select group of leading syphilologists who included Thomas Parran, soon to be Surgeon General of the PHS, and this group sought to classify, evaluate, and to treat patients with syphilis and to compare a plethora of different treatments. But they were unable, this group, to overcome disagreements with clinicians about ways to evaluate syphilis and syphilitic patients and unable to function effectively without a stable source of funding, which was not available for human subjects research before World War II.

Now I would suggest that one could detect a desire for methodological rigor in the organization of what is arguably the best known and/or infamously known study of untreated syphilis in Negro men in rural Alabama. That is of course, the Tuskegee Syphilis Study. This was a study, I am sure the audience and the panel knows well, begun in 1932. But in order to set up a prospective study, these researchers from the VD division consulted leading experts, including many of the people in the cooperative clinical trials group about inclusion and exclusion criteria for participants in this study. And also forward thinking for the time, selected a group of 199 men to serve as a control group in a prospective study of the effects of untreated syphilis. This is not to provide any defense of the Tuskegee Syphilis Study but to point out what the desire was to create an advanced form of medical evaluation.

So this represented advanced thinking in 1932, even though at the same time, the inclusion criteria were not systematically funded. And as Susan Reverby and Jim Jones have pointed out, it is really not a study of untreated syphilis but of under-treated syphilis because they enrolled many men who of course had undergone treatment and there was no

written protocol. So I am not holding it up as a model of methodological rigor but a work in progress.

So I ask you to compare, for example, the organization of a clinical trial with a new treatment for tuberculosis in 1946. This was a coordinated effort by the National Research Council attempting to bring in groups from the Veterans Administration, the Army, the Navy, and Public Health Service to evaluate the use of streptomycin in tuberculosis research. But the VA, for many reasons, was unable and unwilling to allow a control group. And it is not because they didn't understand that a control group was particularly important but the political fallout of withholding what might be an effective treatment from veterans was deemed unacceptable.

Now they also understood that spontaneous recoveries made evaluation of data more problematic. And certainly they had the wartime experiences with penicillin that showed — I mean, so they had that experience in the treatment of syphilis. And sort of the difficulties again, of pointing to and standardizing patient selection, stage of disease, and so on. So the study of streptomycin at the VA ended up with no control group.

Although the Public Health Service was committed to the control group, they had a much smaller study and were able to enforce standards and rigor and many people thought that this came up with reliable generalizable information about the effectiveness of the efficacy of streptomycin.

Now treatment studies and non-treatment studies differ of course from studies in which researchers seek to infect participants with a pathogen. The advent of the germ theory of disease in the nineteenth century encouraged hundreds, if not thousands of efforts to establish that a particular germ caused a particular disease.

Just one example, not American, but Gerhard Armauer Hansen, the Norwegian researcher, identified the bacillus of leprosy now known as Hansen's Disease. But less well-known, that is, in order to comport with Cox principles, he injected the bacillus into the eye of a female patient who complained and brought suit against him. He was fined. He lost his privileges in treating patients. However, he retained his post of scientific director of research.

The efforts to conduct such studies responsibly, that is in the deliberate infection of people, are well-known and include studies in such colonial possessions of the United States as Cuba and the Philippines. Therein, U.S. military surgeons developed written contracts with so-called native populations that were available in the native languages, in order to avert

controversy and political scandal. And I refer to Walter Reed's efforts with the Yellow Fever Board, to the work of Strong, Sellards, and others in the Philippines who made contractual agreements available in sort of the native Filipino dialect for the benefit of the prisoners taking part in studies of cholera and plague vaccine.

Now I use the word responsibly here, suggesting efforts to avoid creating legal and popular criticism. I do not mean to imply in any sense that the use of these what I will call non-Americans was necessarily respectful. Anyone who has read Paul de Kruif's *Microbe Hunters* cannot escape, and it is a well-known example, but the dismissive blatant racism and ethnocentrism of researchers and research products involving non-white, non-American subjects. And I would suggest that in some cases, that disrespect did more to sour relations than so-called responsible research practices.

So very briefly, some of you may recall that in 2002, the American Association of Cancer Research took the unusual step of renaming its prestigious prize for young investigators. They essentially stripped the name of Cornelius Packard Rhoads from the prize. If little known today, Rhoads was an enormously important figure in twentieth century biomedical research. During World War II, he held a number of important posts and he was able to convince sort of funders to create the Memorial Sloan Kettering Institute for Cancer Research. He was considered central to it.

Perhaps less well-known, at least until 2002, was that in 1932 he was a young pathologist detailed to the Rockefeller Anemia Commission in Puerto Rico. He had a very difficult transition from New York City to San Juan, lots of personal difficulties and problems with his subjects, which culminated in a letter that he wrote but never sent, a letter which came into the hands of Puerto Rico laboratory technicians and eventually into the hands of Puerto Rican nationalists seeking independence from American rule.

I won't read you the entire letter but just to give you a flavor of it, "Puerto Ricans are, beyond doubt, the dirtiest, laziest, most degenerate, and thievish race of men ever inhabiting this sphere. What the Island needs is not public health work but a title wave or something to totally exterminate the population. I have done my best to further the process of extermination by killing off eight and transplanting cancer into several others."

Although multiple investigations of Rhodes and these claims led to no evidence that he had killed patients or transplanted cancer into them, his language, his attitude, the threat of racial of extermination persisted, not surprisingly, for decades.

In 1950 for example when two Puerto Rican nationalists attempted to assassinate President Truman, they referenced Rhoads' letter and the efforts at race extermination. And in 2000, the AACR, the Association for Cancer Researchers, responded to the story by appointing an ethics inquiry and ultimately a decision to remove his name from the prize altogether.

Now one of the issues surrounding the deliberate infection of individuals with disease that I would suggest deserves greater analysis, may be the special status of sexually transmitted disease. There are suggestions that the studies of syphilis and gonorrhea prompted extreme anxiety during World War II and perhaps they still do. I mean, one question might be if the Public Health Service had deliberately infected people with hepatitis, would we have the same degree of response?

Certainly deliberately infecting American prisoners with gonorrhea provoked some of the lengthiest and most detailed interchanges among researchers funded by the Office of Medical Research in World War II. And members of the National Research Council believed that inmates of federal penitentiaries would turn out to be far superior as research subjects for a potential study of gonorrhea prophylaxis and treatment. Superior to the inmates of mental hospitals, who could not offer meaningful consent. This is from a 1944 discussion. Superior to civilians who could not be trusted to comply with the needs to avoid sexual conduct for six months. And also superior to both military prisoners and conscientious objectors who were deemed not necessarily cooperative with the aspects of the research.

Still, officials at the NRC debated whether or not adverse public reaction about deliberately infecting gonorrhea would cause a loss of prestige for the entire enterprise. And in the end, they reluctantly approved them, although it turned out to be somewhat anticlimactic in that reliable means of producing gonorrhea in the prisoners turned out to be absent. One other small historical consideration I put forward in —

DR. WAGNER:

Susan, we are a little under two minutes.

DR. LEDERER:

Okay, yes. I am almost done.

The special status of sexually transmitted disease is the familiarity all syphilologists in this period would have had with the deliberate infection of neurosyphilitic patients with malaria. And I would just remind people that in mental institutions, it was common practice to use some inmates

as biological containers of malaria bacilli in order to treat people down the road. So this was a common, common practice.

Concern about adverse public response was the rationale for keeping many experiments out of the public eye. Certainly this was one of the key findings of the Advisory Committee on Human Radiation Experiments, which found in many cases that in order to avert public controversy, rather than for purposes of national security, and I would remind this audience that it wasn't only concerns about human experimentation but the more politically volatile issue at the time of using dogs in radiation experiments. The 1966 Life Magazine expose about organized pet theft rings prompted more mail than the abuse of human subjects or even the Vietnam War.

So in conclusion, secrecy, syphilis, standards of responsible conduct and responsible science, the development of these standards, science, ethical and governmental, has been uneven, contested, inconsistent within government agencies, and changing over time.

I would just remind members of the Commission that the Guatemala study is unlikely to be the only such study out there lurking in the archives, hidden in the file drawers and library papers. These yet to be discovered studies will also be evaluated in light of ongoing efforts to understand past practices in human subjects research.

And I will conclude by saying I think Faulkner was right to say that the past isn't dead, it's not even past.

DR. WAGNER:

Thank you, Susan. Our next speaker is — yes.

[Audience Applause]

DR. WAGNER:

Professor Dan Brock is our next speaker. He is the Frances Glessner Lee Professor of Medical Ethics in the Department of Global Health and Social Medicine, Director of the Division of Medical Ethics at Harvard Medical School and Director of the Harvard Program in Ethics and Health. A busy fellow.

Dr. Brock served as a staff philosopher on the President's Commission for the Study of Ethical Problems in Medicine and was a member of the Ethics Working Group of the Clinton Task Force on National Health Reform. He has been a consultant in biomedical ethics, health policy, and numerous national and international bodies, including the National Bioethics Advisory Commission and the World Health Organization.

Dan, we are pleased you could join us last evening. We are especially happy to have you address us this morning. Welcome.

DR. BROCK:

Thank you for the invitation. It makes me feel old to be here because it was 30 years ago that I attended my first meeting of the then existing President's Commission as their staff philosopher. So I assume that there are even some people in the audience that weren't alive when I came the first time.

I am not going to talk much at all about Guatemala either. I have read a little bit about it, but obviously I haven't gone through all the cartons of materials that you are going through. I do think it is worth saying that I think it is pretty unlikely that that kind of thing could happen now and that is a good thing. Now I am not saying it is certain that it couldn't happen now, but if we think back that was 1946 to '48. That was just after the second World War. We had been sensitized to these issues because of experience with German atrocities. But those issues simply hadn't been on the table at that point in any comprehensive way the way they have been now.

The examples that Susan mentioned were all post that period. The various commissions that have addressed these issues are all post that period. The whole oversight process with IRBs and the work of the Commission in the mid-70s was all post that period. And I think we can pat ourselves on the back a little bit, maybe kick ourselves in the rear at the same time, but pat ourselves on the back a little bit that the things that have happened since Guatemala have at least improved the prospect of a thing like that not happening again. I am usually not that optimistic but —

I was asked to basically talk about the basic conditions for research being ethical. Now you do have among your commissioners someone who could do this much better than I, namely Christine Grady, because I am going to draw largely on a paper that Christine wrote with Ezekiel Emanuel and Dave Wendler that was called What Makes Research Ethical? So this is basically the beginning level discussion of these conditions.

They identified seven requirements in their paper. The first was what they called value. Why do you need this? Well because you are going to use scarce resources and you want to avoid exploitation. You don't want to be doing something that doesn't have promise of any value in particular to the community in which it is being done. You don't want to put subjects at risk without a potential for benefit. That I think is fairly uncontroversial.

Their second requirement is what they called scientific validity. This is necessary to get what is supposed to be the product of this research, mainly generalizable knowledge. So in a way, this is a way, this is a scientific norm but it is also an ethical norm because if you don't have scientifically valid studies, you are putting people at risk for no potential benefit.

The third condition was what they called fair subject selection. This is something that Christine has written about independently, too. I have used her stuff when teaching. The subject selection needs to be on the basis of the scientific goals of the experiment, not whether the people are easily available, vulnerable, and so forth. So for example, much of the drug testing in the 60s and early 70s was done in prisons at that point. And that was not because the prisoners were the ideal scientific subjects, that is because they were there and they were easily available.

Basically you want a selection to minimize the risk to subjects and to maximize the potential benefits to the subjects. So we, for example, have had major efforts in recent years to include as subjects people who had been either excluded or under-represented: women and children, minorities, because you want to have results which are relevant to them. A fourth condition was what they called a favorable risk-benefit ratio. You want to do two things there. You want to, in order to make it as favorable as possible, you want to do things to minimize the risks. So for example, that will include what your exclusion criteria are for the study and you also want to maximize the benefits. That is, you want to make that risk-benefit ratio as favorable as possible.

Initially, it is an assessment of the risks and benefits to the subjects. Where I think IRBs have more trouble, at least the one that I was on for 15 years, is when what one is trying to do in measuring the benefits is to measure the benefits of the potential knowledge that may come out of the study and how that knowledge may be useful over time. It is worth noting the fair subjects condition was violated by Guatemala almost certainly. The favorable risk-benefit ratio was violated in some cases by Guatemala, as I understand it. So, it is fairly easy to condemn Guatemala on the basis of conditions like this.

A fifth condition in their paper was what we call independent review. This again, I think, didn't happen in the case of Guatemala. It is to minimize the conflicts of interest that can exist between researchers and potential subjects. It is also important for maintaining the public confidence in the research enterprise. As you will say it is, you don't want conflicts of interest but you don't want appearances of conflicts of interest as well. It also gives you social accountability of the risk for the research and the researchers.

The sixth condition is the one that gets all the attention in many cases, voluntary informed consent. This is — We almost don't need to say anything about this. This is to ensure the self-determination of the subjects and that they have made an informed choice and a voluntary choice to participate. This, too, was violated in Guatemala certainly in some of the subjects that were used.

And their seventh condition was a little vaguer, I thought. But in any event, respect for potential and enrolled subjects. So one of the ways one shows this is by properly maintaining confidentiality. There are a number of other ways in which one shows this. You are showing that you are dealing with human beings, not chairs that we just sit on without asking them if we can sit on them.

Now and they added in a later paper the collaborative partnership, which we heard considerably about already today. There is a follow-up paper which I would just, I mean, Christine was one of the authors of it, too, point out to you, specifically directed at what makes research ethical in developing countries. And there they developed 31 benchmarks for the assessment. I don't think I have time to go through 31 benchmarks, so I don't intend to.

Let me just mention what I think are four of the main controversies which need to be addressed. I am not entirely confident you can settle them, but you can at least address them. And these are, I think, all familiar to everyone here. One is the issue about standard of care and basically the controversy there has tended to be: is it a global standard, best anywhere, or a local standard? What is the standard in this context? My own view is that the right answer to that is something between those two and I won't take time to say how it gets between.

A second issue is placebo-controlled trials when there is beneficial treatment. The FDA likes placebo-controlled trials and they encourage them being done. And they are necessary, in some cases, to give you the information you want, which is, is this better than nothing as opposed to is it as good as or — as some alternative. But the proper place for placebo-controlled trials is one of the areas of controversy.

A third is one that was talked about earlier this morning, namely, care for somebody after the study. Now it is interesting. If the study shows that something is beneficial, then that should be made available to the subjects and some people then go on and say to the community, to a country. One of the issues there obviously is what is the scope of that obligation? The other aspect of the scope of it is how long does it last? I mean, with antiretrovirals for HIV, if you have to provide them, you have to provide them basically for a lifetime for people. So it is how much, and to whom, and from whom, that that ought to come.

It has always seemed to me if we want to recognize people's participation in research and recognize it by giving them something of value, this condition only recognizes it in cases of successful clinical trials. Most clinical trials are not successful. And so there is nothing that comes to people for their participation when the clinical trial doesn't result in establishing the successful treatment. So it has always seemed to me a somewhat strange way of recognizing people.

And then the final condition I will mention is the issue of ancillary care, which is especially important in developing countries. Ancillary care basically is care that is usually not necessary for the study but it is discovered in the course of engaging people in a study if they have other medical needs. And needless to say, that is more important in a very poor developing country where there will be more other medical needs that haven't been adequately treated.

And so the issue here is what is, again, the scope of the responsibility of researchers to provide for the ancillary medical needs of subjects? That again in developing countries, if that responsibility was extremely broad, then it would no longer be as much more cost effective to do the studies in developing countries than it is now. One of the reasons, as we have talked about earlier, that a lot of research is shifting to developing countries is because it is cheaper to do it there. If there was a strong enough obligation to meeting ancillary needs, it would not be as much cheaper as it is now.

So thank you.

DR. WAGNER:

Thank you, Dan.

And our third speaker on this panel is Eric Meslin, founding director of the Indiana University Center for Bioethics, Associate Dean of Bioethics in the Indiana University School of Medicine and a Professor of Medicine, Medical and Molecular Genetics, Public Health, and Philosophy. He co-directs the Indiana University and is it Moi? Okay, thank you. Moi University Academic Research Ethics Partnership, a Fogarty International Center-funded collaborative research and training program jointly based in Indianapolis and Eldoret, Kenya.

Dr. Meslin is the former Executive Director of the National Bioethics Advisory Commission and the Bioethics Program Director for the Ethical, Legal and Social Implications Program at the National Human Genome Research Institute. He is an appointed Knight of the National Order of Merit by the President of France for his contributions to French bioethics policy and we are really fortunate to have you here. Thank you.

DR. MESLIN:

Thank you very much.

DR. WAGNER:

A truly international individual.

DR. MESLIN:

Thank you, Dr. Wagner and Dr. Gutmann. Members of the Commission, it is a pleasure to be here on this side of the table. So I do want to thank Val Bonham and the staff of the Commission. There aren't many who know what you go through. So I may be one of the few who do and I am grateful for the invitation and also grateful for you remembering that there was a Commission now ten years ago that was interrupted by a Commission in-between. So there is a legacy that this Commission is continuing and I am grateful to participate in that.

In April of 2001, NBAC submitted to President Clinton its report on ethical and policy issues in international research. One of the first, if not the first, extended discussions by a government advisory group on this topic in the world. It was exhaustive but not comprehensive and it identified several key ethical and policy issues facing researchers, institutions, regulators, sponsors, and others. And it makes a number of recommendations, 27 in total, on many of these issues.

Later that same year, NBAC, as it scurried to complete its work before its executive order expired, completed a second report on research involving human participants, focusing on the domestic issues facing the United States. I was asked to speak essentially about both of these reports but given time, I am really going to focus only on the international report and I would be delighted to take questions about the other one.

In the decade since those two reports, a comprehensive literature has emerged documenting a number of developments in the international health research and research ethics landscape including, among other things, the amount of research conducted by whom and where, developments in ethical guidelines, in oversight mechanisms, the maturation of several difficult ethical issues, the emergence of new topics, and examples of excellence.

Before I speak to those developments, I do want to remind us, as has already been done by my colleagues to my left, that these developments in research ethics need not be seen through a single myopic lens. In fact all research, all science is undertaken through a much larger geopolitical and often economic lens. We should not forget, for example, that in the context of certain world events since 2001, we ought to reflect on how they have affected our views, including such things as 9/11, two wars, an international economic collapse, the public health responses to SARS

and pandemic influenza, and a number of natural disasters that have befallen the world.

Now in my remarks this morning, I would like to highlight in honor of it being ten years since these two reports, ten of the developments in international research ethics over the past ten years. They happen to be from my own personal list, although everything that I am saying is substantially supported in the literature and I am happy to provide that in my extended remarks to the staff.

The first development is that the volume of international health research has grown and the locations have shifted. The number of international clinical trials conducted has increased, as has the number of research subjects enrolled in studies around the world. The number of FDA-sponsored studies has grown, the number of investigators working in other countries filing applications for investigational new drugs in the U.S. has increased. The number of countries in which research is undertaken has expanded with substantially more growth in economically developing countries than developed countries.

From these facts we might conclude that there has been a changing geographic breadth of research which calls for a special attention to social, cultural, and political issues in any assessment of the ethics. It places a greater emphasis on how to answer one of the questions that has come up a couple of times this morning: namely, what is the justification for conducting research in a country other than the one from which the principle investigator comes?

This expansion also calls the question that research is not motivated solely by science or by health or addressing global inequity, which are legitimate and often touted justifications, but a concern that the interest is in conducting studies in countries with lower barriers to entry. The second development — And this will be the pattern of my remarks, quick development, a couple of conclusions, and then hopefully time for questions. The second development is that there is more funding from more sources. There is more money being spent by the NIH with more foreign awards made, a couple of dips over the period between 2004 and 2008, but there is more money coming out of the NIH.

There is more money being spent by pharmaceutical companies and more by these companies than by federal governments actually. There is more money being spent by philanthropies and charities. Clearly the Bill and Melinda Gates Foundation plays amongst the largest roles but there are many other philanthropies and charities around the world who are also participating much more than they did ten years ago.

There is more money being spent by NGOs and there is more foreign aid, not a lot but there is more foreign aid than the U.S. provides, some of which comes in the form of support for health research.

These facts suggest that not only does money influence the conduct of research, and we would be naive if we didn't think it did, it also influences how priorities get set and by whom. It used to be a pretty simple equation, the golden rule. Whoever has the gold makes the rules. Well if federal governments were those that provided the vast majority of funding, then clearly they would have the ability to identify their priorities for research. But when other players and partners start to participate, priority setting also changes.

A decade ago, we were actually struck by the injustice of the 10-90 gap, that only 10 percent of health research spending went to diseases that affected 90 percent of the world's population. Now while some funding is being provided for rare and neglected diseases that leak into that 10-90 gap, it still substantially exists. This panel is titled social issues and justice issues and this is for many of us, one of the most profound issues of injustice with respect to research and has nothing to do with the type of the study. It is what gets to be studied and who gets to decide.

The third development is the diversity of innovative arrangements for conducting and sponsoring research. It used to be the single investigator getting an R01 or a program project grant might be the model, but clearly we know that that model has long ago given way to many other innovative collaborative proposals, not the least of which is that there are more public-private partnerships that extend well beyond the traditional federally sponsored or even pharmaceutical company-sponsored trials. As has been alluded to earlier, the use of prior agreements in the pretrial setting has become a much more common arrangement now than ten years ago and we are now seeing them as being used much more regularly as a key component of research partnerships. I will remind the Commission that ten years ago this was a bizarre idea. There were two papers in the literature in 1999 about prior agreements and it was seen as a very odd, legalistic maneuver. Well now everybody seems to do it. Well, we should not lose track of that fact that this is a positive development.

Now these innovative funding development arrangements have been proposed to lower the cost of and actually increase the access to previously unaffordable drugs. And guess what? That is actually happening, not perhaps as fast or as comprehensively as we would have liked, but it is happening. Some of this, of course, is a result of pharmaceutical companies developing their own humanitarian pots of money and making medicines available for lower or even free, for free cost. But still, the arrangements are changing the nature and scope of

collaborations and the attended power relationships between and among sponsors.

The fourth development is the exciting growth of community engagement practices. Again, ten years ago we didn't talk about engaging the community or public advisory groups. We didn't talk about community advisory boards as a key component of designing research. We are doing that now. The traditional model of informed consent, one person being given information by one researcher, is becoming far less common in international research.

We have a lot of experience in Kenya using barazas, which are community meetings. Deliberative democracy strategies are being used in places as far away as Western Australia engaging aboriginal communities. So we are seeing many different kinds of arrangements. It may be too early to tell whether these models improve the process and outcome of research but the potential for growth and innovation is really exciting to watch.

A fifth development has been the way that the harmonization debate has evolved, stalled, and then evolved a little bit more. More countries have developed or substantially updated their own national guidelines. Our own Office for Human Research Protections now compiles a list of international and national guidelines. And it now numbers about a thousand laws, regulations, and guidelines for more than a hundred countries from Argentina to Zimbabwe.

We are seeing more specialized guidelines developed for specific types of research: embryonic stem cell research, biotechnology research, biobanks, privacy, and genetics.

We are seeing more international and transnational organizations who are developing or updating their own guidelines. UNESCO, WHO, CIOMS, the World Medical Association and the ICH have regularly updated their documents, as have other groups, such as IAVI and UNAIDS.

Whereas, a decade ago we were reminded about the ethical peril of applying a double standard to research, we now may be approaching a situation where multiple standards exist and may divide along regional or national lines. Ironically, the growth of policy documents in more countries has made it harder to achieve consensus on substantive matters of ethical acceptability, even when there are general agreements about the particular items: informed consent, risk-benefit, confidentiality. The devil truly is in the details. And the fact that more countries have Federal Wide Assurances with the U.S. may actually alter in fundamental ways the sovereignty argument that many of them had

been claiming for so many years. Let our country have our guidelines for our people. That is being mixed around quite a bit now.

A sixth and closely related development is the way that the standard of care debate has matured, but consensus has still not been achieved, as Dan and many others this morning have mentioned.

The initial debates arising from the ACTG-076 study concern the definition and application of the concept and then about which standard ought to be adopted. Dan alluded to and maybe you will ask both of us during the question period what this kind of compromise seems to be that people are moving towards, somewhere between highest possible and local. These are just terms that are used but it turns out that if we take the wrong position, we may be unintentionally discriminating against many people. So we ought to be quite careful.

I am happy to report, though that the debate has matured beyond these ideological extremes. And it would be nice to sort of pose the question rhetorically. Would we be having the same discussion about the ACTG-076 study today if the proven standard of care was an affordable one? I'm not sure it would be the same discussion.

The seventh development is a somewhat more foundational one. Again, Dan alluded to it a little bit but it is really the deeper understanding of key ethical issues and principles that we have observed over the last decade. Some of these questions about whether there is a necessary set of ethical principles about which we can all agree, whether this agreement is even possible or needed.

Interestingly, the Belmont principles, those ancient principles that have achieved some would say, I think Ruth Faden characterized it in the ACHRE Report as achieving almost constitutional status, have actually been exported quite happily all around the world.

Many actually think Belmont are the rules for the United States. It is a fascinating discussion, we can get into it later. But it is showing us that this claim of U.S. ethical imperialism needs to be modulated somewhat. There are many other principles and because of time, I want to pick up a couple of final topics. I will say that the topic is quite large.

Responsiveness to health needs as a justification for conducting research was very dramatic and sort of unusual when NBAC first talked about it 1999-2000 but now everybody talks about responsiveness to health needs, as if it were so obvious, why are we even debating it? The Commission is not, NBAC shouldn't take credit for that, but it is nice to see that people were paying attention.

The eighth development, in contrast, recognizes how institutional procedures and policies for ethics review have evolved. There is more ethics review committees in more locations around the world. In fact, what is very exciting to see is that there are other models now being proposed: regional IRBs, central IRBs, ethics review systems. From this we might conclude that the expansion of ethics review committees reflects a trend towards national efforts to assess and review protocols but it also affects our recognition that the current model of dual review might need to be revisited.

The ninth and ultimate development may be the most exciting and partly I owe it to Barb Sina and the people at the Fogarty Center for this, and that is that there are many more dedicated training programs around the world that have emerged and expanded focusing on research ethics capacity building. Not just Fogarty but UNESCO, WHO, the Wellcome Trust, the Gates Grand Challenges, all require the importance of building bioethics research capacity as a part of building science capacity.

So there is much more to do. I know that I have run out of time and I will maybe save my final tenth development, which are my cases of excellence for questions if we have them. Thanks very much.

DR. WAGNER:

Very good. Again, thank you and thanks to all three of our speakers. We really appreciate this.

[Audience Applause]

DR. WAGNER:

I will go ahead and acquiesce to the request that the two of you have made that we ask you about the spectrum of standard of care from highest possible to local. Dan, you want to start with that one? All three of you, of course, can contribute.

DR. BROCK:

Sure. Actually I credit Dan Wikler who I have discussed this with because this is basically his view. One way of thinking about what we should expect in developing countries is to ask well, what is the standard of care in countries that are at a similar level of economic mostly and also cultural development, the countries that do best who are similarly situated. Now that will often be considerably better than the country in which the trial is taking place. So that is one way to try to begin to think about how do we identify and justify a middle ground. Because basically we justify it by saying look, comparable countries do better than you do. They have a higher standard of care. It is reasonable to expect that of you because you are a comparable country. So that is the general line I would take.

DR. WAGNER:

To look at comparables.

DR. BROCK:

Yes, which always exist.

DR. WAGNER:

Eric?

DR. MESLIN:

Yes, I would echo Dan's points and make a couple of others. The debate actually began on a bit of a misunderstanding, I think, between our legal colleagues who when they hear the word standards, think about minimum requirements below which if one falls one might be exposed to either liability or other claims of unethical or illegal behavior.

So the term standard sort of set us off on a path that was very difficult to get back from. I think we have gotten back in the way that Dan has described.

The one thing that I would add to his remarks that hasn't been said yet is there is a lot at stake in deciding what we want to say about this term. On the other hand, if we are going to become so committed to getting the term right, we may find ourselves in the untenable position of having to accept the outcomes of a debate and deliberation that we might not want to have. Setting too high a bar, which might be not only ethically aspirational but some might say morally obligatory, why shouldn't everyone be entitled to the best, it is sort of an intuitive response, might put us in the position of saying well we just can't pay for it. Therefore, the fairest thing is that nobody gets it. I would hate to see the debate digress to that. So seeking middle ground with ways of supporting or as they say ratcheting up other forms of benefit might be the way to get to the middle.

DR. GUTMANN:

I would like to ask a follow-up to that and it really is I think fundamental to what a commission is charged with doing and can do in recommending two government and society practical standards, as opposed to or as at least distinct from ideal standards.

So ideally, we would not have the world we have today. I mean, let me just — It is just, I think, an ethical fact, as close to an ethical fact, a complex one, because we would disagree about what ideally it would be but I think nobody, I would postulate nobody in this room thinks we have the ideal world.

So the question I have is can you give examples and Susan, Dan, and Eric, I would like each of you to give examples of where you think the ethically optimal standard, which we should know what it is, diverges from what you think should be legally required of medical researchers or

of the process which goes forward before one advises a government to allow research to go forward.

Dan, you write about this. You teach about this. Why don't you begin?

DR. BROCK:

Well I got stuck in your question about legally required. A lot of the things, the norms that now govern research, don't really have that status of being legally required. And to some degree, that is a good thing because it enables a discussion to take place, an international discussion, and sometimes you get a consensus out of that, sometimes you don't. But I think the example that we have talked about, the standard of care example, is one where I am not sure who has the authority to make the law but there could be developed a consensus on a process to evaluate the standard of care in different countries and then a consensus that if Merck wants to come in or Pfizer wants to come in and do studies there, it has to meet this middle ground that we were talking about. And it wouldn't bother me if that was legally required but I think it is probably better required by the —

DR. GUTMANN:

Let me say why it is required, just so you understand. I think and you can correct me if I am wrong, that all of the things that made the Guatemalan experiment horrendous and wrong ought to be forbidden today. And if they are not forbidden today, we as a Commission ought to recommend that they be forbidden.

Now I want to know what beyond the things that should be — You know so there are things that should be forbidden and then —

DR. BROCK:

Right.

DR. GUTMANN:

— there are things that we should aspire to and expect.

DR. BROCK:

Right. After going through those, Christine's and Zeke's seven principles, I then turned to four issues that I think there is no consensus on and they fall under this.

I think, too, that the things that made Guatemala clearly wrong ought to be legally required but in the examples that I used of ongoing debates, I don't think there is a consensus certainly present now and probably maybe not likely in the future on which one could say well, this is now what we want to legally require. So, in a way, the legal requirement asks

for a stronger consensus that this shouldn't happen. And we can use cases like Guatemala and others to identify those.

The trouble is that the things that were bad about Guatemala, in a way, everyone now agrees were bad about Guatemala. And so I think —

DR. GUTMANN:

That is a good thing, wouldn't you say?

DR. BROCK:

Yes, that is a good thing, right. But it then doesn't provide too much new work for the Commission because you have already got that consensus.

DR. MESLIN:

So I would just add two quick things. In your restatement of your question, it sounded like you were alluding to standards beyond just the "standard of care" debate, —

DR. GUTMANN:

Yes.

DR. MESLIN:

— which for the longest time had been about placebos or not placebos or what do you get.

DR. GUTMANN:

Absolutely.

DR. MESLIN:

And I think I actually like the way you phrased it because focusing on standards and limiting it to a particular research design, we have had that debate. You shouldn't just declare placebos unethical. It is like declaring oxygen unethical. It has no context. Right?

So it is much better to have the discussion what are the standards that we might be able to agree on. Whether it is Emanuel, Grady, Wendler, and everybody else, or whether it is Lavery's, there is a bunch of lists out there. And of course, lots of groups have come up with these: prior review, consent, adequate assessment of risk and benefit. We have been having that debate for a while and I think to be quite provocative, I think that debate is over. What are the items about which everyone can agree? The challenge is figuring out how we are going to interpret and apply them in countries on a daily basis. Well I will give you a very concrete example.

At Moi University, which is in the Northern Rift Valley in Kenya, where we have had a 20-year partnership between the IU School of Medicine

and the Moi University School of Medicine, we have been building this capacity for 20 years. We had a workshop in 2003 talking about common areas in research ethics. We all stood up and identified our common areas and everyone agreed informed consent, very important.

Assessment of risk and benefit, very important. Where was the disagreement? Well one of our colleagues in Kenya said of course informed consent is very important. However, you realize that in some studies women should not be allowed to give informed consent without the prior approval of the male head of household. Now there is an agreement about the principle of informed consent. No debate. The disagreement and the challenge about which you cannot set a standard, a specific line in the sand, other than a procedural one which, you know NBAC went on this, the Nuffield Council went on this. It is how are you going to decide? Are you going to walk away from the table and say we don't agree or are you going to try and figure it out?

I would like to suggest that there has been a lot of very healthy figuring it out over the last ten years, a lot of good success stories.

DR. WAGNER:
Christine.

DR. GRADY:
Well thank you all for very interesting presentations. And I think sort of what I wanted to ask falls right into what you were just talking about, Eric.

It struck me as you were talking that, I mean Susan laid the groundwork for you know, over time what we think is the major issue to address changes, as does the landscape of what is going on at any time.

Dan talked about four things that he thought ought to be attended to in terms of issues that haven't been completely resolved and I agree they haven't been. But I also agree with Eric that in all cases, all four of those cases, the debate has matured considerably and some of that is attributable to what NBAC did and what people did subsequent to NBAC. So I guess my question is, at this point in time looking forward what do you think the issues are that this kind of body should focus on?

DR. MESLIN:
I have got two that I will suggest. One is an effort at real international harmonization. And what I mean by real international harmonization, I think we had mistakenly blurred the harmonization debate into one about homogenization. Everyone has been talking with trying to get the same document.

I think what this Commission can do and follow in the footsteps of all the last four prior commissions, is to start really thinking about how it positions itself amongst its colleagues in the world.

So there have been summits of bioethics commissions every two years for the last ten years. They have been very, very productive meetings but they have not resulted in an international consensus on significant issues. We are now at the policy, you might want to call it the translational policy research, as opposed to clinical translational research. There is a policy valley of death out there. And the valley of death is that we have got lots of great reports and then we have lots of things we like to do and we don't have a way to translate fantastic ideas into action. And I think if this commission chose, it could leverage its considerable respect internationally into thinking about how it can offer proposals and learn from others. That humility is something every commission learns.

The second thing is that — I'm sorry.

DR. GUTMANN:

I am going to ask you to hold your second thing because that will be an answer to the question that I am going to ask the panel of presenters and we have to stay on time because we are absolutely committed to having time for public comment at the end.

So if I could ask —

DR. WAGNER:

Doctors Corey and Califf to return.

DR. GUTMANN:

— Doctors Corey and Califf to come to the table please. Okay, Dr. Califf to come to the table, please.

For the audience's sake, what we are going to do now is ask the presenters, and Christine asked the perfect segue question, to advise us as a Commission, given their varying and deep expertise, the following. I will pose a simple question. Which is, if you had to name it, what is the single issue? So Eric you got a pass. You get two because you have one already. But what is the single issue that you think that the Commission should address in its report in response to President Obama's charge that we advise the government on scientific research, the ethical standards of scientific research moving forward. Or if you will, what is the single fact that you think we must emphasize in our report. And before I ask you all to answer, I would just ask the audience and my fellow commissioners to thank you very much for a wonderful set of presentations.

[Audience Applause]