



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT
Implementing Federal Standards

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DR. GUTMANN:

Thank you all and I just wanted to thank Christine Grady again for a wonderful presentation. We're ready to get started on our next session two. This session's on implementing Federal standards and it's a natural sequel to what we were speaking about earlier. And let me begin without further adieu in introducing our first speaker. Connie Celum is a Professor of medicine, a Professor of Global Health and an Adjunct Professor of Epidemiology in the Department of Public Health at University of Washington. She's also Director of the University's International Clinical Research Center. Dr. Celum is a renowned infectious disease professional and Epidemiologist. Her research interests include HIV Prevention Studies in Uganda, Kenya and South Africa, as well as Herpes Transmission Studies in countries including Peru, South Africa, Botswana and Kenya. Most of her research is conducted through international collaborations. Welcome, Connie, you are on.

DR. CELUM:

Great. Thank you so much. It's really an honor to be here, and I have to say I feel humbled, there are many people who could be giving this talk. What I'm going to try to do is give you an overview of some of my experiences over the last 15 years, really focusing on the last 10 years where I've been doing more international research. And I will be focusing on HIV because it's the area that I've sort of devoted my professional life to and want to give the good news that I think is coming out of the report that UNH put out the end of last year that actually, for the first time we're beginning to see declining HIV incidents in many, not all, but many African countries and some are starting to use the ubiquitous term, the tipping point, that we may actually be at this point where we're seeing decreases. But I think we need to realize we need to continue to work hard to not lose that tipping point and we need to increase coverage of testing, treatment, and continue the march to find new effective prevention strategies. And research is clearly a very important part, I think, of the decline and can continue to be an important part of the public health response. And I just want to highlight that an example of this is paper, the New York Times coverage last week and in the last year of the use of anti-retrovirals for prevention. We now have data that suggests using gel or a pill can protect people from becoming infected with about a 40% efficacy. Those studies were done in young South African women, as well as men who have sex with men in the Americas, as well as Thailand and South Africa. And the exciting news that caught people's attention last week that treating infected persons also has a powerful impact in reducing their transmission by 96%. So we're really at this point where as the cartoon shows, we really are having a paradigm shift. That these drugs can actually not only provide clinical but also public health benefits. So I'm going to give you a preview of my conclusions and hopefully back

them up with some of my comments. From my perspective, from the studies I've been involved in either leading or part of as an investigator, I do believe that sitting in 2011, that international clinical research can and often, I'd say almost always, is being implemented to highest ethical standard. However, I don't want to trivialize the amount of effort that goes into doing this and I will highlight a few of the many challenges and barriers to achieving this. One that's been talked about earlier is tremendous issue for most of us doing multi-center research, that there are multiple layers of review, and you sometimes get inconsistent recommendations and you have to try to harmonize those. I think that we have an understandable conservative approach that we need to sometimes, I think, examine that, that is, do we approach things more from the medical versus the public health perspective? I think that some of that conservatism leads to substantial delays which do cost lives and money. I am a full believer that collaborative capacity building research is essential. I would not have been able to do the studies I've been involved in without this. And I want to end on one area that I would encourage the Commission to think about is again with the focus on HIV that given that the incidents is highest, prevalence is very high and incidents is increasing among women and I think that the approach to inclusion of pregnant and breast feeding women is an area that needs to be focused on. So just a snapshot, I trained in San Francisco with very heavily influenced by the impact of HIV in my clinical training, the first in the '80s and early '90s focused on Epidemiology, some more observational data collected on sexually transmitted infection and HIV among gay men both in the U.S. and Peru, and moved into a desire to find intervention, so I've work in the areas including HIV vaccine research, behavioral interventions, and then I highlighted in bold the three studies I think really had a very big impact on me as an investigator because I was having to lead them. And the first one was an NIH funded phase three trial, a suppression of genital herpes to try prevent people from becoming infected, enrolled over 3,000 people from 9 sites, three continents including the U.S., Peru and Africa. And we did a sister study that was funded by the Gates Foundation that was trying to ask the parallel question: could you suppress herpes and make someone less infectious and reduce transmission as well as disease progression? To ask that question required testing the intervention in serial discordant couples, and that was a study that in 14 sites and 7 countries in East and Southern Africa and I'll come back to that. And lastly, an ongoing study that is looking at: can we prevent risk of HIV-negative person becoming infected by using the anti-retrovirals for prevention in the negative partner? And this is a study of almost 4,800, of discordant couples in Kenya and Uganda.

So, principles and reality of international HIV prevention and vaccine research. I have felt strongly that one of the first questions is that we should always be testing interventions that can be delivered, if effective.

Hence, early studies on generic acyclovir. That working in the number of countries I've worked in, it is very clear that people are poor, stigma is still a real issue and they have limited access to healthcare. So they are vulnerable populations and we take that seriously.

One of the things that I've always been amazed at and challenged by is that we're trying to help people, who may have a sixth grade education, read and understand an eight page consent form before they commit themselves to go through monthly visits for two years. But I think we have staff that do that and do it extremely well.

The IRB reviews is a challenge and I'll come back to this when we get into the details of one study.

Insurance coverage: not all countries, but some require it. Some funders have to be convinced that we need to do this.

Sounds like we will be coming back to genetic questions, but use of stored samples and international settings is a sensitive issue, especially for those that are, when you mention that, you and the consent forms for stored samples, that you plan to do genetic studies.

The standards of care are not static and they evolve and I think that sometimes rational people interpret them differently and expect researchers to either really directly provide the services so there is some tension here sometimes. What should we do that once male circumcision is shown to be effective, should we refer, do we actually have to pay for it and now with the good news about treatment, what are our obligations as researchers to provide that?

And then I think similarly, I think Dr. Corey eluded to this one in his comments about HIV vaccines as just what are our obligations if someone becomes infected during the study; do we provide the treatment, do we make linkages? So these are a few of the issues. And then if you find something effective, what are your obligations to provide it after the trial is over?

So the first study just briefly, I won't go into details, but the study looking at could you suppress herpes in an HIV infected person and reduce risk to their partner, was a study of 3,400 couples, but that means almost 70, multiply times two in terms of the real sample size, because we did follow both partners in the couple for up to two years. This was a study that was done in 14 sites and 7 countries in East and Southern Africa, and the primary endpoint to measure efficacy is did the HIV negative partner acquire HIV or not based on whether their partner was on Acyclar or placebo.

And I thought it might be helpful to just say what does it take, in that single slide you can't tell what it takes to do a study. So we estimate, based on the data we could collect from our sites about 55,000 couples of unknown status were tested across these 14 sites. So there's a public health intervention right there. Out of those 55,000, we identified 6,500 that were serial discordant and 3,400 were enrolled. The other remaining couples were ineligible. And the sites and the couples did an amazing job. We had higher retention than anyone thought was possible and drug adherence was very high. And this requires an incredibly motivated team. Just to give you flavor of what it looks like to recruit those couples, a lot of the work is really getting couples to be motivated to know their status as a couple, which should have happened by now in epidemic, but hasn't. There are a lot of challenges and barriers with these sites, to have really found solutions to those barriers.

And what did it take to actually do this in terms of the implementation? We were doing this in a university, so we did not outsource this. We took the whole responsibility to do the study so we built a coordinating center, we prepared 14 sites, 7 had never done a clinical trial, so we had to build the whole infrastructure. 20 IRB reviews of the initial protocol and one protocol revision translation and back translation, you want to make sure your questions are asking the right thing into 16 languages, 6 informed consent forms, three each for the positive and negative partner and over 300 case report forms. Over half million forms faxed, 2 million samples collected, a third of which came to Seattle to make sure that the things we were testing were right and hundreds of site visits and monitoring visits and conference calls.

We learned a lot through that study. We learned herpes suppression of the dose we use didn't actually achieve our outcome. But we found that actually serial discordant couples were very common and that there was to many people surprises there was about 50/50 chance in these African sites that if one person had HIV that their partner was negative.

We also found about a third of almost a third of infections came from an outside partner, even in what we were calling stable serial discordant couples, and we provided monthly counseling and drove down the risk to about 2%, where past studies have shown 8 to 9%. So we really just by being in the study, people's risk came down. But we also found out for couples wanting children, their risk is high.

So that led us to do the study that is ongoing. We are one of the last 3 studies that is looking at the question about using anti-retrovirals for prevention called Prep. In this study, we and others will have data in the next 2 to 3 years and these data from these studies will inform whether

or not these drugs should be used in HIV negative partner to prevent acquisition.

But I want you to realize that none of the studies are testing this very potentially potent intervention in pregnant and breast feeding women. We do monthly pregnancy testing and as soon as they are identified to be pregnant, their study drug is stopped and they include adolescent women in high risk in Africa. And that is just the picture of that study designed now. Now 9 sites in Kenya and Uganda.

But I want to just highlight a few things that I really do think that part of the things that never make it into manuscripts is the amount of effort that goes into really building capacity. These sites, as I mentioned in both our studies with couples, half the sites have never done clinical research. So it meant, intensive training, not just about study protocol, but about HIV, about herpes, about the drugs, as well as human subjects, good clinical practice, good laboratory practice. And the laboratory infrastructure's very weak in Africa, so we literally built laboratories to do monitoring visits. Now, every 6 months, every single consent form is looked at by an independent monitor, as well as many of the clinical records.

The part that I enjoy the most is the capacity building. We find that just awarding small grants of \$3,000, \$5,000, you can actually stimulate investigators, young investigators to come up with their own questions. And we've also built, and I think learned a lot about couples' counseling and this is just an example, by seeing what it looks like when you go to someone's home to do that kind of counseling.

This shows you just an example of going from an old district hospital that looked like a bombed out building to a new clinical research site in 6 months. And just to show you where the drug is stored with the highest quality of procedures, as well as data records are stored. These are really impressive sites.

Now just end on a point that I think is worth attention by the Commission, which is, I feel there is a real imperative for finding new biomedical prevention strategies for women during pregnancy. The risk of HIV acquisition is high. The risk of perinatal HIV transmission is high if a woman becomes infected during pregnancy, much higher because her viral load is so higher. And I think it's fair to say that pregnant and breastfeeding women are one of the largest underrepresented populations in particularly in HIV prevention research given the burden that they bear. I think there are real general liability concern if pregnant and breast feeding women are excluded from studies. It ensures a delay by doing the sequentially, and obtaining critical safety data, and it relegates providers and often patients to be using second-line drugs if we

don't have safety data early enough. And I think there is some real issues around harmonization between Federal agencies.

60% of infections in sub-Sahara and Africa in women during pregnancy, colleagues have documented 13% incidents in western Kenya. 13% chance a woman would acquire HIV during pregnancy and our study in couples showed both a twofold increased risk of transmission and acquisition during pregnancy.

So I think there are a number of questions and I'll just go through these quickly because I think my time is up. But I think some real scrutiny of what constitutes minimal risk: do you have to show efficacy in non-pregnant adult through with FDA approval before a drug is studied in pregnant women? And then, if that is the case, how will safety data be acquired once it is used widely? And I think we need to really think about the appropriate balance and caution and proactive collection of safety data because these products I can assure you will be used be it a microbicide or other products if they are shown effective.

And I think there are also issues related to paternal consent of HIV infected partners of pregnant women, HIV infected pregnant women and I think all these issues require some more scrutiny.

So just to summarize, I think internal, international clinical research can and is being implemented to the highest ethical standard. There are substantial efforts required to do that and multiple barriers and challenges. I think we need to work towards more efficient, coordinated IRB reviews for multi-center studies. Cliff Lane at the NIH is trying to look at the feasibility of the joint or external IRB review for international research. I think that may be not totally acceptable for some African IRBs, but we need to look at it. I think there needs to be a needs assessment of international IRBs and I think we need to continue to focus on the essential aspects of collaborative capacity building research and then as I mentioned at the end, evaluate barriers to including pregnant women and breastfeeding women in research. And harmonize those efforts.

But, at the time Obama was being inaugurated, I was in the village where his grandmother lived and I thought the motto on secondary school that he opened as a Senator is the right one that we do have model of endeavoring to excel.

So I just want to end with a quote from one of my favorite African proverbs and thank the many people who've educated me along the way.

DR. GUTMANN:

Thank you very much, Dr. Celum, thank you. Our next speaker is David Borasky Jr. He is the Institutional Review Board Manager in the Office of Research Protections at RTI International, it's a major private research institute with private and publicly funded activities around the globe. David Borasky has more than 12 years of experience managing Institutional Review Boards in the United States and facilitating training activities on basic research ethics and IRB operations and function. He is a member of the Board of Public Responsibility in Medicine and Research and he has served as a consultant for the WHO, the U.S. Department of Energy, the NIH's Fogarty International Center and numerous other institutions. Mr. Borasky is a co-author of the award-winning Research Ethics Training Curriculum and the Research Ethics Training Curriculum for Community Representatives. He has provided hands-on assistance to IRBs throughout the world, specializing in capacity building activities for IRBs in low resource settings. Welcome. MR. BORASKY: Thank you, Dr. Gutmann, and Dr. Wagner, members of the Commission it's really a privilege and a pleasure to have the opportunity to talk with you today about the challenges of implementing the Federal standards for the protection of research subjects. I'll be addressing the issue from my perspective as an IRB professional.

In this role, I spend most of my time working with researchers and IRBs to ensure that research is conducted according to the principles of the Belmont Report and in compliance with the applicable U.S. regulations. In addition, as you mention I spend a great deal of time over the last decade providing technical assistance to IRBs in low resource settings at institutions collaborating in federally funded research and expected to adhere to federal standards. There may be a little overlap in my comments and the comments of Dr. Grady this morning, but you can consider them exclamation points or underscores, I think a lot of great points were raised in that presentation.

So I'd like to begin by taking you back in time to the late 1990s, early 2000s. In the 1990s, the most prominent enforcer of the regulations governing IRBs was the NIH's Office of Protection from Research Risks or OPRR. And at that time the Director of OPRR would frequently repeat a mantra, that's a professional IRB meetings and training conferences that said if it is isn't documented, it didn't happen. And this was always said in the context of talking about how detailed IRB records needed to be in order to achieve compliance with the OPRR interpretation of regulations and in response IRBs appropriately began to tighten up their operations.

At the same time, OPRR was in the midst of taking numerous actions against institutions that were determined to be out of compliance with

the federal standards. These actions included suspending federally funded research, an action known as a shut down. In many instances, this was due to findings of administrative noncompliance and subject safety was not always an issue. This certainly got the attention of the IRB community and the leadership of institutions that were implementing research.

In 2000, OPRR was dissolved and a new office, the Office for Human Research Protections or OHRP was established within the Department of Health and Human Services, and at that time many believe this was in part because of the heavy handedness of OPRR, and there was hope that the change may lead to a more collegial relationship between regulators and implementers.

So what you may wonder was the focus of the new regime? I would say in a word, it was compliance. And presentation at the time of the rollout of the new office, the OHRP's responsibilities that they promoted included implementation and interpretation of federal regulations and policy and "evaluation of compliance."

The new OHRP identified its overarching concerns in the form of questions like: is there a "culture of compliance?", Are IRB members and investigators knowledgeable about regulatory requirements? And is there adequate documentation of IRB findings and actions? Application of the ethical principles was largely absent from the discussion and this regulatory focus compliance approach set a tone that exists even today.

So what was the result of this emphasis on regulatory compliance? The result was that the IRB community put itself on the compliance express. This was expressed in both good and bad ways, on the good side: the work of IRBs gained recognition and there was much needed professionalization of the field. Leadership at research institutions had to sit up and take notice of the IRB, nobody wanted to be on the receiving end of a suspension. The idea of a comprehensive human research protection program gained traction and there was a renewed emphasis on training and basic research ethics for IRB members and researchers. In addition, best practices and IRB management emerged, and people in my line of work could now obtain credentials as certified IRB professionals.

But there were problems when one peered over the top of his or her rose-colored glasses. Obsessed with compliance or with being found noncompliant, IRBs cast a wider net, reviewing more activities than ever before. If it looked like research and quacked like research, it was going to the IRB; better safe than sorry. Critics in the research community took notice and decried the mission creed that was evident everywhere,

especially in non-biomedical research. IRBs were now reviewing oral histories, journalism projects, student projects, this was especially again difficult for the non-biomedical research community, because IRB review meant compliance with regulations that were written primarily in response to ethical lapses in, and for the regulation of biomedical research.

While the regulations themselves offered a great deal of flexibility, particularly for research in the social sciences, many IRBs were afraid to take advantage of the flexibility because it required largely subjective decision making on the part of IRBs and there was an aversion to making a decision that might be questioned by the regulators.

Another bi-product of the emphasis on compliance that affected how federal standards were implemented was the emergence of accreditation of IRBs and HRPPS. While accreditation may be beneficial to some institutions in their HRPPS, there is concern that the accreditation standards disproportionately emphasize regulatory compliance over quality of ethics review and accreditation sets the bar higher than what is required by regulations.

So, that's the current context in which the Federal standards are implemented or at least, that's how I perceive it. And I'm going to talk specifically about challenges related to implementation. And the first challenge would be to determine what we mean by the Federal standards. In general, when talking about the regulations, we tend to lump them into 2 groups: the Common Rule and the FDA regulations, much as Dr. Grady described before. Well, the latter are fairly discrete and clear, research and FDA regulated drugs or devices are going to trigger the requirements found under 21 cfr 50 and 56 and 312 and 812 and others.

The Common Rule on the other hand, is less so. While the basic subpart A language founded 45 cfr 46 has been commonly adopted by many federal departments or agencies, they are, in fact, separate regulations that emanate from different points of authority and lack common understanding and enforcement. While we tend to think OHRP has enforcement authority over the Common Rule, the truth is that their jurisdiction is limited to research conducted or supported by Health and Human Services. In addition, Common Rule departments and agencies have not uniformly adopted subparts B through E.

So, for example, under the current US AID regulations, a common rule signatory, there are no additional protections for children, prisoners, or pregnant women. USA ID has not adopted subparts B,C, or D. It's therefore possible that NIH and US AID could independently fund identical research involving these populations, and there would be

drastically different regulatory requirements for each. Does this make one study more ethically sound than the other?

This patchwork quilt of Federal standards is confusing and difficult to implement for institutions, investigators and IRBs seeking to comply. In addition, there are U.S. departments and agencies that conduct research but are not signatories to the Common Rule. And research that is privately funded and does not involve FDA related product is not subject to any Federal oversight or regulation. An astonishing gap.

My conclusion on this point is that applying Federal standard in the absence of truly common rule is challenge in and of itself, or to use Dr. Wagner's language: "our house may not be in order."

Another area implementing Federal standard presents challenge to researchers and IRBs is the regulatory requirements for informed consent, obtaining the voluntary informed consent of potential research subjects is a cornerstone protection. However, concerns about regulatory compliance, institutional liability and outside demand such as HIPPA and GINA have hijacked informed consent and replaced informed consent as a vehicle for protecting subjects with informed consent as a vehicle for protecting institutions.

While it is true that there is inherent flexibility in the informed consent regulations, they are routinely abandoned by IRBs that are afraid of accidentally missing something or admitting that one bit of information that could be of potential importance. Too often the default is to include everything.

The current Federal standards are largely the same as they were 30 years ago. At that time, the research environment was very much focused on the institution, hence the idea of the Institutional Review Board. The regulations did not anticipate the move to collaborative multi-institutional, multi-national research, nor has it evolved to keep up with the times. Rather than assess and revise the regulations, the system relies on interpretive guidance from regulators that describe alternative IRB review models. In addition, we've seen the emergence of the independent or commercial IRB system.

However, even with this guidance and availability of alternative models of IRB review, many institutions still insist on local IRB review and oversight even when they're one of perhaps, dozens of IRBs reviewing the study and even when the nature of multi-state research often means that the protocol must be more or less accepted as is. IRB review of protocols by multiple IRBs is cumbersome, counter-productive, and without evidence, showing that it provides greater protection of research subjects.

Finally, I'd like to talk for a few minutes about challenge of implementing the federal standards in an international context. As is the case with multi-site research, the regulations did not anticipate international research. All of the challenges I've discussed are equally problematic and at times more problematic in the global the context.

For example, foreign institutions who receive funding from HHS are required to apply for federal-wide assurance. There is an international version of the FWA that provides foreign institutions with the opportunity to identify which standards they will apply in the oversight and conduct of research. Several international standards are listed in addition to the U.S. regulatory standards, implying that the non-U.S. standards are suitable for research covered by a foreign institution's FWA. However, this isn't the case. In 2006, it was noted in the Federal Register that "For HHS conducted or supported research, all institutions holding FWA and engaged in such research, must comply with requirement of 45 CFR Part 46". That compliance is required regardless of whether the institution marked other procedural standards on the FWA form. As a result, foreign institutions conducting HHS funded research are expected to understand and apply the U.S. Federal standards, including all current guidances, interpretations, and nuances even when there are highly regarded local standards and a robust research ethics infrastructure.

Applying the Federal standards for informed consent while taking into account the challenges I described previously is also problematic in the international context. On more than one occasion, I have sat in on meetings of international IRBs that wonder why they are being asked to approve the California experimental subjects Bill of Rights or a HIPAA authorization form or a consent form that advise subjects to report problems to individuals and institutions located half a world away. While problems of this nature can be comical and often corrected administratively, there is a more serious problem when a 15 page consent form is required for use in populations with low literacy. Or when a signature is insisted upon in settings where signing a piece of paper is usually the precursor to bad things happening. There is something disingenuous about giving somebody a copy of their multi-page consent form after they have indicated their willingness to participate with a thumb print because they are incapable of reading or writing. Again, a laser light focus on demonstrating regulatory compliance trumps the common sense that I imagine the drafters of the Common Rule would have expected IRBs and institutions to apply. So I'm going to stop there and look forward to the discussion with the Commission. Thank you.

DR. GUTMANN:

[mic off.] Thank you. Center for Health Policies and Ethics that is currently involved in research ethics, educational programs and among other countries Argentina, Brazil, Columbia, Costa Rica, Jamaica, Honduras, Mexico and Peru. Sergio is also a member of our International Task Force. He is currently involved in the responsible conduct of research for biomedical investigations in the Latin American region. Dr. Litewka is also the Project Director for the Pan American Bioethics Initiative and the Latin American Director of the CITI Program, a web based educational initiative for research ethics. I'm going to shut the...

DR. LITEWKA:

It's working. I am really honored for this invitation and I am really grateful for the opportunity of being here. So, many thanks to all the Commission for bringing me this wonderful opportunity.

As Dr. Gutmann said, I'm among other things, Director of some initiatives based on University of Miami, and those are related to Latin America and the Caribbean. So what I'm going to is focusing mostly in what is my experience and the work that we have been doing there. This information is probably not totally accurate, but because it's very difficult, as was mentioned before, to have broad knowledge about all the research activities that are being carried out elsewhere. But in any case, it's significant. I think it's an approximation about what we find in the Latin American and Caribbean region in terms of the investment made by the NIH and also by the pharmaceutical companies. And what is important, in my opinion, is that if you see the countries that are, I don't want to use the word less developed, but with less infrastructure in terms of research, also they have the least investment in terms of research by the pharmaceuticals. However, the NIH is playing the big role there. And when I'm saying that it's playing a big role, it means most of the research that is being carried out in the low resource countries, in Central America and the Caribbean, are generally oriented towards problems that are focused on health issues.

Other countries, like Costa Rica has become, where for a long time have for international research, however, I would probably mention that later. Costa Rica is no longer in this moment a trial site because all the trial activities have been suspended by the Costa Rican government and that has to do probably about the way to trying to address difficulties in terms of governance in the research enterprise.

So one of the things, many of the things have been mentioned by my colleagues before and I will address again some problems that create big gaps in the understanding of how to implement or to harmonize Federal

standards in the Latin American context. And I think that could be also applicable probably also in the United States what it has to do with informed consent.

Most of the complaints about informed consent, it has been mentioned before, is that all the regulation implies that all informed consents have to have legalistic approach, very legalistic approach that in many case it's not well understood by the subjects. And on top of this incredible amount of pages that many subjects have to sign, not necessary they are informed, but they are signing. There are also the local requirements, which is probably translation of what the informed consent want to said, want to say, attempted to say before. So there is not a very comprehensive disclosures of risks and eventual benefits in terms of all the consequences of the research. And indeed and again, this could happen in Latin America, but also in many other places here. It's related to reason of therapeutic misunderstanding, mostly because most of the people who are being enrolled, if they know that they are enrolled in a clinical trial, sometimes they don't understand about which phase of the study are they involved in and whether or not that may have some sort of positive expectation in terms of his or her health conditions.

IRBs, or research ethics committees in the way they are known in the Latin American context, also are facing several problems. For example, lack of clarity about what is defined about exam studies. And mostly the overarching problem probably is lack of resources for IRBs and when we are talking about lack of resources, we are talking that not only for whether or not their members are receiving any stipend or something like that, but the infrastructure needed to make an IRB work effectively: that means computers, the way to track records, and the way in which the minutes are being taken, periodicity of the meetings, and misunderstandings and that is related also with lack of education and support in terms of research ethics. For example, clinical ethics committee, this is something I saw many times, clinical ethics committees that eventually work as research ethics committee and they change their position.

As you know, many foreign institutions are starving for cash. I mean, they need money. This is not again exclusive related to Latin America, but in many cases local IRBs have the conflict of interest because if they reject the study their institutions will not be funded. And if they do that, they will be outcasted and probably replaced. So this is a big, big problem that we have to keep in mind when we are addressing how to harmonize what we are requesting.

Because of the lack of resources the way in which confidentiality and privacy is assured is very sometimes it's at stake. Many records are more

public than you should want to see. And basically the oversight of clinical trials also is at stake because if you don't have resources to follow up, it's much more complicated that you can know what is happening in the future.

But not only are the infrastructure problems in many countries have a total absence of specific regulations for protection of human subjects. So they have some guidelines coming from the Ministry of Health or sometimes from medical associations or scientific association, but we are talking about guidelines, not talking about real rules or regulations. Brazil, has to be mentioned, probably is the most evolved country in terms of having Federal laws. But aside from Brazil, most of the Latin American countries are facing a problem in which they have in some cases they don't have any regulation at all, which is the case of many central Americans in Caribbean countries and they are working on that. In other cases, they have what is known as normative polyphony, lots of regulations, overlapping one with the other and again maybe that is not exclusive for those countries, but in any case they have different jurisdictions, because they are not Federal laws. They are competing with Provincial regulations and even depends on which agency is overseeing the research, if there is that.

But in the case that even you have regulations, the other point, who has the oversight of those regulations? And this is another important problem here because it's not only having regulations, as it was said before, but also how we do enforce those regulations?

But other challenges that the Commission will face for sure is how the investigator is accountable and if some research misconduct is already happens or at least there are suspicions that might happen. And also which is the accountability of the foreign institution? Not only the researchers but the institutions as a whole.

Transparency is another problem. Some countries are addressing some activity. For example, if you go to the website of the Peruvian Ministry of Health they are doing now an effort by their INH, their Institute of Health, in making public all the records for the research that they are doing and the funding, where it is coming from. However, again there is a lot of continuing to do that. Brazil, is trying to do that since I remember at least 2008, and still we don't have a website in place in which you may have that.

But transparency also has to do with the lack of public trust in the research enterprise. And here I want to mention something which I think it might be important. Some countries are suffering serious problems of governments -- and when I'm saying governments, I'm not talking about governments in terms of the research activity in itself, but

the whole concept of the country itself. So if the regulatory quality is at stake on the rule of law, it's complicated and the accountability of the institutions that it's also difficult to be exercised. And the voice of the community is not listened. Maybe we have also to consider when we are talking about regulations about aspects that have to do with the whole picture of the problem. And take that in account when we are thinking in harmonizing regulations with different standards that have to do with not only cultural issues, but with social issues which is more important. So because of that, one of the things that has been -- also other discussion has to do if there is lack of trust in the research activity. The use of placebos is also questioned many times because the idea of having people vulnerable, that is being used for goals that are not necessarily related to them, it puts another question which is definition of vulnerability. And again, I think we have to address the concept of vulnerability, not only in terms of minorities, but in populations that their voices are not sometimes being listened or their community has not a real representation in the political situation. I think that's all for my part. Thank you very much for the Commission.

DR. GUTMANN:

Thank you so much, Sergio.

I'm going to extend this so we have time for Commission questions for 10 to 15 minutes and then we will break. And I will recognize now, I need to correct something I said earlier because we have some wonderful participants here and the philosopher Frances Kamm came up to me at break and when I said we walk a tight rope, let me just say that sometimes that tight rope has equivalent things on both sides. For example, take Tuskegee: sometimes when we under-regulate, we fail by letting people die who could otherwise be saved. And sometimes when we over-regulate, we let people die who could otherwise be saved. Absolute equivalence.

But sometimes on one side of the tight rope is, in under-regulating, we let investigators actively harm people, and on over-regulating, we let people die who could otherwise be saved. Those aren't exactly the same things morally speaking and it's important to look at. And the reason I bring this up is sometimes the will of over-regulators is a very good will, which is to prevent people from actively being harmed. And they judge that to be worse than failing to save people who could otherwise be saved. So I just want that to be on the record because I think there is important distinctions here.

Having said that, I want to recognize Nelson Michael and I will keep my list. Yes, which has everybody on it. (Laughter) Okay. Right.

DR. MICHAEL: All right, Sergio, I'll remember that. So I really want to thank all three of you for wonderful presentations. Most of your

comments were directed at the higher level guidances and some of the issues that occur to that, but each of you in your presentations also -- I think in your case Sergio, I think you really hit the nail on the head -- but all of you addressed this to some degree: What as we look forward to the next several decades should we do to strengthen good participatory practices? So we focus on those regulations that we as investigators or funders or regulators need to deal with. But what can we do to codify the rights of participants so that when you have a 15 page informed consent document, there is at least some normative process that all of us could potentially touch and strengthen that part of medical research, especially as it involves the kind of work that you do Connie, and errors where you work.

So we know that UNAIDS and the AIDS Vaccine Advocacy Coalition have published guidelines on good participatory practices, but it's pretty much in an infant state. So I would like to see what your reaction would be to taking that form of approach to try to strengthen medical research as we go forward? Because then I think we might be able to find a pathway to make investigators and regulators more likely to look at populations like pregnant women and breastfeeding women.

DR. LITEWKA:

Let me tell you, I wish I could help the whole answer, but just . . .

DR. GUTMANN:

We do, too.

DR. LITEWKA:

We all. One thing that I noted and again you have to probably some bias because the level of funding is totally different in the pharmaceutical industry and the NIH funding in terms of the magnitude of research. However, as we saw in the graphic before, the NIH commitment is quite high. There's one thing, if you notice, most of the allegations of research misconduct, at least coming from Latin America, came from the pharmaceutical. I'm not making any particular answer, maybe they have more sites, maybe -- but there are more problems related to the pharmaceutical industry. And I didn't hear in the past 15 years, any allegation about research misconduct in terms of NIH funded grants.

Maybe that's by chance, but maybe there is some difference. And there is one big difference: when you do research under NIH, if you want to have a grant -- regardless where you are, regardless in which country you live - - you have to follow a mandatory training program. Maybe it sounds naive, but I'm not selling my own program which is the CITI, but could be any other. You have to have some program, some education activity that at least teach you, even researchers they don't like that, IRB members they don't like that. But they have to do that.

And the idea in that is other than regulations, there is some moral foundations for those regulations. And also educations create awareness. I mean, sometimes you do, you commit some transgressions, not because you deliberately are looking for doing that, but because you don't know. But when you have some basic training that shows you that some things cannot be done, that creates a sense of common accountability in some regard. So I'm not saying that education is total, but I think that having some similar standards in terms of education could be one way to address the problem.

DR. GUTMANN:

Thank you. David, Connie. Let me just go down quickly if you would because I want to get as many questions and answers in as possible.

DR. CELUM:

So I think my response would be in part – I think it would help the field if there was some way to publish and distribute Best Practices. I mean I've read the UNAIDS guidelines and I think sometimes they're still, it feels removed from what you really have to do in the field when there is an issue, be it something like the standard of care is evolving. And I think it would be useful to think about a way to actually do that and distribute it so that when you take your human subjects training online, you are not just being reminded of the regulations, but actually thinking of case studies, like a case study approach.

Then I think a second part, and maybe this happens and I just am not aware of it, but I think there is a real need for some of the most contentious issues -- like for an example in international settings, taking samples where you're consenting that there will be future research, including potentially genetic studies -- there needs to be a place, a mechanism to have discussions with international IRBs. And I think that at least in my institution we've done a lot of training for example with University of Nairobi IRB. But it would be helpful to think, is there a way regionally perhaps to really bring IRB members and have some discussion about what is the best practice for doing genetic research so that there isn't just this kind of automatic antibody response when people see something that says genetic research in it.

DR. GUTMANN:

David.

MR. BORASKY:

You know, I think as you were asking that question I was trying to think of models where research is done in some of these settings with effective community engagement or community participatory activity. I think there are some really great models out there. The HIV Prevention Trials

Network has a mandated Community Advisory Board component. There's nothing in regulations about that, but they put one in place. The CAPRISA Program in South Africa that does a lot of this cutting edge research has a great community engagement piece with standing Community Advisory Committees.

But absent that, the regulations aren't helpful and I don't know if creating more regulations would help. But right now, IRBs have to have a nonscientist member and nonaffiliated member and often they're tagged as community members, but that is not really what they are meant to be. I think we could look at some of the programs that have been successful and turn them into best practices and to think about how those could be encouraged by sponsors.

DR. GUTMANN:

Lonnie.

MS. ALI:

My question, thank you. Good. My question is for Connie. Thank you all for a wonderful presentation. When you talk about medical versus public health perspectives and it leads to substantial delays -- and we've had a lot of material that we have read where we talk about protections for the individual versus protection for the community, and what leads to protections for the community and what's best for the community -- can you just elaborate a little bit about that? Would that be a result of these consent forms not understanding, people not trusting what is being presented to them, who was actually presenting these consent forms to them?

And then on the second thing I wanted to ask you about, when you are talking about the populations that are not represented in these studies, the pregnant women, breastfeeding women and just looking at your slide and seeing all the things that you have to go through to get those participants to engage. Is there a particular reason why -- besides maybe they think there might be some harm done to them because they are pregnant and with child and don't want to introduce some kind of medical intervention that's pharmaceutical or some sort -- is there some reason why they are left out?

DR. CELUM:

I'm sure there are other people who could give more higher level answers to the first question because I'm a clinical researcher, I don't make claims to being a studied bioethicist. But it seems like -- the background materials were really helpful, actually. I thought they laid for me a framework that you sort of don't get when you take these online courses. And like, how did we get here?

I do think that a lot of the research ethic came from therapeutic trials. And when you move into prevention trials, I feel this even as a tension when I'm talking to colleagues, they say, why do you need 3,000 people? Well, it's because in many populations, for an example, studies with gay men, there's maybe a 5% risk per year that someone will get infected. The study, the CAPRISA study it was 9% in women, but it's still low. It's not like a treatment study with cancer or someone who is HIV infected where 100% of people are at risk for the outcome.

But there is a different, I'm not sure if I can address your question from a perhaps an ethical perspective, but from an implementer's perspective, it means absolutely you have to have community engagement because when you think about what it means to do research right now one of the hardest populations to reach would be men who have sex with men in Africa. Illegal in every country except for South Africa. But I know people who are working in those populations -- talk about a tricky area because you have to have very attentive attention to protection of confidentiality well beyond what's mandated by the guidelines. But I think there is a way in which we've adapted as a research community. I think that we do have Community Advisory Boards. We do do huge amount of stakeholder engagements.

But it is different than when you are dealing with a group of, for example prostate cancer. You're trying to work in communities where there is still a lot of stigma because by being at risk people don't necessarily want to, that's not a label they want to have, that I'm at risk for HIV. So you have to really be very careful in how you move into those communities and do a tremendous amount of preparation before you go out and actually potentially do harm. So I'm not sure if that is really answering your question, that is kind of what comes up.

The second part about pregnant women, again, I ask for ethicists to correct me if I say anything wrong, but I think a lot of that comes from the thalidomide disaster years ago and clearly there is a real desire to not subject women who are pregnant or the fetus who can't consent to potentially harmful interventions. But I think that the lens we look through that needs to be thoughtful because I think for example in our acyclovir studies, even though the American College of OB/GYN say it's okay to use -- in fact they encourage acyclovir in the third trimester -- to reduce congenital herpes, in Africa we decided thinking from, if I were IRB member I'm going to see you're going to use acyclovir, which we don't use a lot in my country. So we just decided we'll stop acyclovir if a women's pregnancy test was positive. That was an ultraconservative approach. I think that many IRB members, they have a checklist they have to go through. You have to have pre-clinical data on pregnant

animals, PK data, and so on. It's just a tendency if in doubt you don't include them. Did that answer?

MS. ALI:

Yeah. Thank you.

DR. GUTMANN:

So final question I have time for is Dan.

DR. SULMASY:

I wanted to return again to the question of the tight rope and to consider another possible downside of the regulatory burden, which is maybe not simply that we're preventing good science from going forward and therefore preventing people from getting help they need, but a point I was raising in the earlier session, there is a sense I think and we'll get your reaction, that the emphasis on compliance and the emphasis on regulation leads in some ways to a sort of cynicism about ethics itself. And sort of also creates an atmosphere, I think, in which the big pictures get missed. So instead of doing ethics, one is doing compliance. So that people don't look so much at the scientific validity of the study anymore, previous data on safety, unique vulnerability of a group of subjects that wasn't listed in the regulations as potentially being vulnerable. Or one study I was involved in on a data safety and monitoring committee, where one site there was 100% compliance – or enrollment in the study, but all the consent forms were filled out, so it was okay. Do you think that that's part of the downside of the regulatory burden? That sort of atmosphere in which ethics itself gets jettisoned and is replaced with compliance with rules?

DR. GUTMANN:

David.

MR. BORASKY:

Well, I think that's definitely a potential pitfall. You know at the end of the day, it's really difficult and Dr. Grady mentioned this, it's difficult to show effectiveness of that an IRB made a "high quality" ethical decision about research. It's real easy to say you get your checklist that says you met the 111 criteria and elements of consent. You know, I do think that it has made many investigators, particularly those that have to deal with multiple IRBs and see the delays that Connie is talking about, highly cynical about the system of protections that we have because at the end of the day, they see they are jumping through bureaucratic hoops. And, you know, anecdotally I certainly often hear from our researchers at my institution that what is the IRB proving by moving this paragraph here in the consent form? Does that really make this a better, more ethical study? Or is that them doing busy work to show they did something?

At the same time, it's so difficult to prove effectiveness of IRBs or quality. I mean, you can try to quantify how many people have been harmed in research and is that due to poor IRB decision making or by bad investigators who are going to do what they want to do? The IRB world has chosen to focus on customer service and time turn around of IRB approval as a measure of high quality.

DR. GUTMANN:

I just want to on behalf of the whole Commission thank Sergio, Connie and David for really an enlightening set of presentations. We will reconvene at 1:15. Thank you all very much.