



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

Commission Members

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James Wagner: I believe the commission is present and assembled, so let us get underway. In this next hour and 15 minutes, we will be addressing three subjects. It is interesting. All are sort of the place-based considerations. They have to do with place where research is done. The three subjects are equivalent protections, community engagement, and site selection. Christine, I don't know. You had sort of stepped out, but Lonnie, Nelson, and I thought maybe the thing to do would be for each of you to make your brief presentations, and then we will have one grand Q and A system for everyone. Do you want to – Lonnie, you probably ought to begin talking about equivalent protections.

Lonnie Ali: Equivalent protection is the recommendation that was made to the commission as part of a larger recommendation by the International Review Panel. In fact, it was part of the first recommendation to the commission that focused on respect for human subjects in their communities by researchers in all phases of clinical trial design and implementation. As noted by the IRP, one way to show respect for community outside of the US where research with the human subject is an ongoing enterprise and a growing enterprise would be through international dialogue with the US and international bodies to ensure human research subjects are protected. And as part of being good research partners and encouraging this dialogue, the IRP recommended to this commission that US and foreign investors would benefit from clarification of US regulatory exception for foreign protections that are at least equivalent to those in the US, as it is delineated in the Common Rule and as it relates to human research subjects.

And then taking it to the next critical step, investigating how it can be applied, what would be that process to make these determinations? In group discussions, which consisted of Christine and Nelson Michael—I do it all the time—we recognize the importance of equivalent protections being a standalone recommendation as it had been a source of increasing frustration and difficulty for US foreign investors, and actually the frustration was even voiced by some of our own members. Given the significant increase of international research studies that are sponsored or supported by US government, the impact of equivalent protections to offshore investigators has become even more important. The frustration and challenge that arise from equal protection practices and procedures emanate from US federal laws that regulate all research utilizing human subjects and is funded or supported by the US domestically or internationally. All such US funded supported research falls under the regulations outlined in the Common Rule. Any agency or institution receiving US funding for human research subjects—I'm sorry, for human subjects research—must follow the guidelines and regulations in the common rule to the letter without exception or waiver.

While this may not be an undue burden for researchers domestically, it does become a burden for researchers who conduct clinical trials in foreign countries, especially given the dramatic growth of multinational research projects funded by the US over the past two decades. Similarly, privately funded research has experienced tremendous growth internationally. Increasing the likelihood of research being conducted internationally can be seen as a result of greater attention being given to the global health needs, as well as to what some cite as the burden, the burden and cost of compliance with US regulatory requirements, although we have been abused of that notion. More specifically, compliance with the Common Rule. This becomes a challenge for researchers conducting studies in other countries that have government regulations and practices in place that offers subject—human subject protections that are comparable, equivalent, or better than those that are in the Common Rule.

Most of these countries follow guidelines for human research protection as outlined in the human–Declaration of Helsinki and Good Clinical Practices. It should be noted that the common rule does allow for US agencies supporting or conducting research to recognize and accept procedures from foreign countries that might differ from US regulations as long as they provide protection that is equivalent to those in the Common Rule. However despite this provision, I don't think there is one example where any foreign country's procedures been accepted as equivalent to those of the US. As it was noted in the IRP report and recommendations, this issue has been discussed by other advisory bodies convened at the behest of the US government, in the past, but none of the recommendations put forth by any of these advisory bodies has resulted in movement by the government on its current position.

In fact, there is over a 10 year history of consideration of US equal protection regulations and their impact on the international research studies, and historically, just to give you an overview, in 2001 the NABC recommended in their report on existing protections for human research subjects that the US identify a set of procedural criteria in the process for determining if a host country's regulations to protect human research subjects that provide the same ethical protections as the NABC. In that same year 2001, the inspector general's office recommended to be OHRP that it address how to better assess other nations laws, practices, afforded equivalent protections to those that apply to human subjects participating in clinical trials in the US. In 2003, the Department of Health and Human Services convened a working group that made recommendations regarding the same issue of equal protections and actually proposed a framework for developing a criterion to determine if both countries regulations and practices offered equivalent protections that are comparable. The first step of that framework pointed out that the Common Rule is actually procedural and doesn't articulate the ethical basis for its regulatory procedures or the actual protections that its procedures provide.

In 2005, there was a Federal Register notice posted calling for public comment on the proposal set forth by this DHHS working group, and the OHRP basically did not take any action on this, so there was nothing ever done. In what might be seen as a lack of responsiveness on the part of the US government, a 2006 Federal Register notice on the interpretation of assurance requirements actually reiterated that any agency or institution receiving government funding or support for domestic or international research using human subjects follow the exact procedures as outlined in the Common Rule. In 2007, there was a request from the UK government to the United States for a determination from DHHS regarding equal protections afforded by the UK procedures for their protections. And other countries are also interested in gaining recognition of equal protections for their protections. However, again, there has been no response, and there have been no answer from our government.

And to date, the Office of Human Research Protections has not formally recognized any country's protections as equivalent. It should be noted that other government agencies are much more flexible, in particular the FDA employs the notion of parity and accepts data from foreign studies that comply with international standards for human subject protections utilizing standards put forth by Good Clinical Practices. And as a result of that, the frustration that was felt not only by the researchers and by people here on this commission, we felt that the recommendations should have two distinct components to address some of the issues that have occurred in the past, or difficulty I should say that occurred in the past.

The first component we thought should work with what was done by the – use the framework that was proposed by the DHHS working group that directs the government's focus to the group's articulation of 7 procedural requirements that are actually found in the Common

Rule, using them to develop a process for evaluating requests by foreign countries and institutions. As part of that, given that all of these recommendations in the past that have been advanced have not been acted on, Nelson suggested that we give them a time limit to respond and to actually implement this, and that was—we are arbitrarily thinking 18 months. Part of the frustration in the past on the part of foreign investigators, institutions, and countries with various government initiated advisory groups has been that the Office of Human Research Protection's silence on the issue of equivalent protections—and because this is the 4th or 5th time this recommendation has been put forth by some form of the government advisory body. The second part of what we are proposing asks the OHRP to respond to why they are acting on a recommendation or why they would not act on it and to keep it as a status, the status of it is. And hopefully we can expect some kind of feedback from them.

Implementation of a process to evaluate other subjects protections submitted by foreign countries and institutions does have some benefit. We believe that it is suggested by the Secretary's Advisory Council on Human Research Protection that it would reduce the burden on international IRB's. They could possibly increase collaboration and dialogue with foreign research partners, show respect for international research communities, ease the burden of regulatory compliance and assurances when engaging in international research. One of the other things that we suggest or that we ask was why had there not been any movement by the government after this have been recommended by so many different groups, and I think a staffer had relayed this to Val—and I hope you don't mind me sharing this—that they were actually waiting for our recommendation. If that's any encouragement.

James Wagner: They say that to everyone.

Lonnie Ali: Well, let us just hope that staffer is correct.

James Wagner: Terrific. Nelson, why don't you talk to us about community engagement and the issues there?

Nelson Michael: So stemming from the first recommendation in the International Research Panel, which focused on community engagement and respect for cultural differences, the recommendation stood on principles that research processes are centered on research funders, research teams, national regulatory authorities, and they are obviously designed to protect research participants, and they include such processes as IRBs or ethical review committees, the informed consent process, and other protections that have been delineated in international subject research guidelines that have been extensively discussed today. And to use Amy's comments on another topic, we believe that these are obviously necessary, but there are not sufficient to ensure the totality of an ethical human subject research environment.

So what community engagement does is, it adds the involvement of relevant research partners to include the research subjects themselves—the communities in which they live and interact to provide a broader framework of exchange between these communities, researchers, regulators, and participants. So in that sense, an effective community engagement process provides an additional layer of safeguards by providing the community with opportunities to more thoroughly weigh and accept or reject the risks and benefits of research activities to discover possible implications of research that might have unintended consequences to host communities, and to independently debate the effectiveness of research protections. This would

be an interactive, continuous dialogue between the community and the research team that would allow for the integration of community norms, beliefs, customs, and cultural sensitivities with research activities.

Community engagement should occur consistently throughout the lifecycle of the human subject research activities by providing a two-way communication between community partners with research funders, research teams, and other stakeholders. So taken together with researcher and research-centered—or sorry, regulator-centered safeguards, community engagement builds a partnership with the broadest range of partners.

So there are important side constraints, and this was something that we mentioned and discussed during our own working lunch to have to take into account for considering all of the possible implications for community engagement. So if the essence of community engagement values the intrinsic ethical position of all research partners, then there is a potential for there to be some concerns if there is a very one-sided dialogue, and not one-sided dialogue could in fact come from the community too, the researchers themselves. Thus if the community norm was to dictate actions that were contrary to any other research partner's ethical positions, such research could not be conducted in the absence of conflict resolution acceptable to all partners.

So in order to get granular and take an additional step forward, we thought that it would be useful to actually point to the single normative body guideline that exists that defines what community engagement is in order to breathe a little more structure into what I just said. So the second version of the document called "Good Participatory Practice Guidelines," version 2.0, that was vetted just this past July by UNAIDS and the AIDS vaccine advocacy coalition, and it was done to provide trial funders, sponsors, and researchers with systematic guidance on how to effectively engage with stakeholders and design and conduct biomedical HIV prevention trials. That's an important caveat I will get to in a second. So this publication provided a tangible roadmap for how one might implement all the highlighted things I just mentioned in the past few minutes, and it is built on principles of respect, mutual understanding and integrity, transparency, accountability, and community stakeholder autonomy. You can see some of these principles are ones that we have highlighted at an independent level.

So one caveat that actually was pointed out during the International Research Panel's deliberations by John was that it is important to understand that all stakeholders must have buy-in to what is considered an intrinsic norm. There may be cases where a community norm wouldn't be acceptable to research funders, as an example, and an important caveat that Christine pointed out was to remind us that these guidelines, even though they are the only exemplar, were built around HIV prevention studies, and therefore, their applicability to a broader range of human subject protection activities is yet to be assessed. So the guidelines, in our view, would need to be prospectively evaluated in that light.

So in our draft deliberations about—within our working group, our discussions within the working group about what recommendations we could put further ahead would be to highlight the evaluation and the specification of good participatory practice guidelines, different evaluative standardized framework, and also to recommend a prospective evaluation of these guidelines because of the generalizability questions that I had previously mentioned.

James Wagner: Thanks, Nelson. Christine, do you want to talk about site selection and the issues therein?

Christine Grady: It was great to work with Lonnie and Nelson. I think if we didn't have the best working group, we had the most fun.

Amy Gutmann: We like the competition.

Christine Grady: The competition was great. So one of the other things we talked about as a working group was site selection, and some of this was in response to the commonly expressed but often disabused notion that expansion of research around the world has a propensity to go to places where rules and oversight might be more lax and people might be more vulnerable to exploitation, so The Commission wanted to consider this issue of site selection and how those perceptions fit in. And I think we talked about the fact that site selection is ethically important for couple of different types of reasons. One is that acceptable sites are those that can ethically treat human subjects and protect them from unethical practices, and that is sort of widely agreed to.

But then there's this other notion of how you select a site for reasons more related to justice and responsiveness. The Belmont report, which was focused on individual subjects, actually has some interesting language that could be applicable here saying that subjects should not be selected because easy availability or a compromised position, but rather for reasons related to the problem being studied, and that justice demands that the fruits of research not provide advantages only to those who can afford them, and should not unduly involve people who won't be able to be beneficiaries. Unfortunately, as we know, there are historical examples of US funded research where individuals were treated unethically and at least in part; this might've been due to the fact that they were chosen because they were vulnerable rather than for the goal of benefiting them or their community.

But it is also important to remember that important scientific and economic benefits come from research wherever it is done, that expansion around the world—expanding research around the world is actually a good thing, and finding efficiencies in doing research, as we heard this morning, is also a good thing. So those create a complicated set of factors in terms of thinking about site selection from an ethical perspective. So we are talking about—we agree actually that protecting and respecting human subjects is the same worldwide, the same ethical principles apply, as we heard this morning from our speakers, and include important notions like not treating people as mere means, treating all fairly and with respect, and not exposing people to unnecessary risk or burdens that are disproportionate to the benefits. And so the sites as chosen for research studies must be able to protect these basic notions. In addition, we have to think about this, worry about minimizing the possibility of exploitation.

So, we are thinking about a couple of different possible recommendations. One is that the commission will reiterate that IRB's and RECs and review committees around the world should determine both that researchers and the sites they propose have the willingness and the capacity to support protection of human subjects at these important levels and/or that such capacity could be built as part of the research endeavor and collaboration that is being proposed. And second, we think this notion of what are the appropriate criteria for justifying the selection of sites needs further study and further evaluation. So we are thinking of suggesting that the government support research to begin to develop operational criteria and guidelines for ethical selection of sites around the world for research.

James Wagner: Christine, thank you. Comments or questions from the commissioners just off the top of your heads? I do wonder, Lonnie, are there ways that we can help OHRP? Do we have any suspicion at all why prior recommendations have gone unheeded? Is there some element of difficulty? Is there some rationale that hasn't been addressed? And why? Why is it they would say, "Well, once this commission reports, we will do it"? I'm wondering if instead of just pushing—maybe staff needs to answer that or help us with that. Do we have any—

Christine Grady: I have a theory.

James Wagner: A theory. We're ready, Christine.

Christine Grady: It is really a theory. I have not spoken to anybody at OHRP, but my theory is that what regulations allow is equivalent protections, and we unfortunately are in a situation where we really do not know how well the procedural requirements in our rules provide protections, so how can we say something is equivalent when we do not know? In our rules. And what Lonnie talked about the working group, the working group met almost 9 years ago, they tried to delineate certain protections that they think emanate from our regulations, but they are not—it's a very useful framework, but they have not been tested or vetted.

Amy Gutmann: So that—whether or not that is correct, let me just address why it strikes me as a peculiar response. If what it means is equivalent protections and not equivalent rules and regulations, then why not just—then we should say what we are talking about are equivalent rules, regulations, processes, and so on, because that is all that the government actually on the face of it can ensure. Otherwise we wouldn't have been asked by President Obama to look at what—whether the protections are there. There are 2 questions. There are the rules and regulations and procedures, which can be equivalent in other countries, and then there is the question of protections, and if the reason is they can't guarantee—we don't know what our protections are here, well, if we don't know what our protections—I hate—this is why I hope this isn't the right theory, because if that is the case, what we are really saying, what the government is saying, is we have all these rules, regulations, and processes, that we have no idea whether they protect people.

Christine Grady: So maybe I should be clearer about what I mean, because I do think—

Amy Gutmann: This is what the problem of speculation may be, but I just want to expose what this speculation is—

Christine Grady: No. I will stand by my speculation but refine it. I think that most people agree, and there are some data to suggest, and there are certainly ethical principles to substantiate, that the protections of the independent review and informed consent do provide some protection of human subjects, and our regulations call for those. But the regulations are very detailed about how those reviews take place, how many people need to be there, how often they meet, how they keep minutes, all those things, and they consent provisions are very detailed in terms of what kind of information, what kinds of documentation, etc. So I think that the problem is what we don't know is whether or not those exact instantiations of how you get consent or how you do independent review are what is necessary for the protection.

Amy Gutmann: So what you're saying—and then I'm going to cease and desist—that what you're saying is basically since we don't know how well these particular things protect, we are just going to assume that our protections are better than others, even though we don't know.

Christine Grady: That is what I think we're doing.

James Wagner: Dan then Nita.

Daniel Sulmasy: Related to that, does anybody else have data about their regulations, rules, etc.? Because of that is the case, we will never have the ability to say that ours are equivalent unless we command the world to do this, as you are suggesting we do.

Lonnie Ali: Dan, let me just say that one of the things we considered was to—because there was the notion maybe doing a pilot study to see if this actually worked, if we can actually do this, but I think the suggestion of whether or not other countries—to look and see what they did in these instances, when research was conducted and they were the host country – how they may have relaxed or maybe not relaxed their regulations, with regards to human research protections. Because maybe that is some kind of the model that we could look at to see how effective it was, but I think Amy goes to maybe the gut of the issue is that if we are actually offering our procedures, we really aren't offering protections, and we may have a bigger issue.

James Wagner: That is true. Nita?

Nita Farahany: So I am hoping to build on that. I'm trying to understand the interplay between the equivalent protections and the community engagement and the difference between procedural and substantive protections. So if community engagement is meant in part to help us recognize cultural differences and perhaps incorporate them, how far does that go exactly? So to John's question, I take it, about the potential intrinsic objections, are intrinsic objections for example things that you cannot do in this country? So for example if marijuana is illegal in this country but legal on another country, and it is because it is culturally accepted and legally accepted in another country, and you are provided the same procedural protections, is that the kind of thing we are talking about? Or for example, in the Guatemala study, where it was permissible to have commercial sex workers but not here, we would think it was wrong to under our laws are under our culture use it. So this conversation around equivalent protections seems to me is not just about procedural protections, but also about the things you can do here procedurally and substantively and then ensuring that same type of protection extends abroad. And right now I'm a little confused just by the conversation we are having and some of the draft recommendations of the subcommittee to the group to discuss about how do these things work together, what exactly are we saying with respect to procedure versus substance?

James Wagner: I think - Nelson.

Nelson Michael: I'll take a shot at that maybe. And this is my own synthesis. I see the equivalent protections being really a dialogue between research regulators saying, “Here are our set of criteria that we use to guide research.”

Nita Farahany: Procedural.

Nelson Michael: Yeah. Procedural. Exactly. Because getting back to the point, do we really have objective information about the effectiveness of each of these regulations? I think the answer there is probably not. So then it comes down to trying to integrate or harmonize between nations regulations that allow research to be done in a more coordinated fashion. Lonnie asked a great question. I think it was the second call we had when she said—and she prefaced her remarks by saying, “Well since Christine and Nelson, you have so much experience in this, what do you know about other nations in terms of whether or not they change their—so if the government of the Netherlands funds research that was done in Brazil, does that work? Is there an equivalent protections process there?” There was a stunned silence on the phone. We had no clue, so I think it gives you some insight into really how much I think we even understand about how constant these procedural issues are across nations.

So that is kind of how I put that into one bucket, is equivalent protections is a recognition that there should be more dialogue and potentially harmonization between procedural issues that guide research. Community engagement I think certainly there is a lot of crossover, but there I see it more and the standpoint of providing a larger fraction of research stakeholders to have a voice in the entire lifecycle of the human subjects protection activity, in terms of the design of this study, the site selection, and in a way it provides a check and balance on the researchers and the regulators to make sure that other stakeholders have visibility into what the thought process is and can provide input from the very design of the study to its final publication or implementation. So I think I would be that more from the standpoint of implementing a research activity.

Nita Farahany: So the question, the reason I'm asking about the interplay of the two, is if there are cultural practices that are—or cultural norms which are different from our own cultural norms, such that research would be permissible in that culture that would be impermissible in our culture, I assume the answer is nothing we are saying here suggests anything about not ensuring that the substantive protections we have here likewise apply when researchers are abroad.

Amy Gutmann: So to take the double negative out of it and make it into a positive, everything we are saying here is consistent with enforcing the same ethical standards. In any community here, there are communities with commercial sex work legal in the United States. You don't have to go abroad for that, so everything—it is consistent with our saying the same ethical standards apply, and the equivalent protections is not an attempt to recognize ethically different cultural standards. It's quite the contrary. It is an attempt—the language on its face is an attempt to say, “There are countries and communities outside of the United States that are unlikely to have equivalent protections to ours judged by the same ethical standards, and it would be good if we could recognize those,” and then there are a set of reasons why it would be good, instrumental as well as non-instrumental.

James Wagner: What prompts the question for me is just getting right back to the report that we are expected to prepare, if we make a recommendation that we think this is a good thing, so long as we are convinced that it is merely bureaucratic lethargy that has kept this from happening in the past, I am comfortable with that recommendation. But if we haven't discovered and can't

address some of the what might be legitimate concerns, then I think we should try to do that and get that into the report before we make the recommendation—you see what I'm saying?

Amy Gutmann: I do, but I think we have the subgroup has recommended something that will help us discover this because as you can see, even our members who are within the government don't know what the reasons are, so what we're asking tentatively here is to if there are good reasons—

James Wagner: - To give us those answers.

Amy Gutmann: —for not ever recognizing any prominent examples of equivalent protections, give them not just to us, they give them publicly so it's like if I invite—say I'm happy to collaborate with anybody. This is a hypothetical, by the way. I'm happy to collaborate with anybody who is equivalently ethical to myself, but I just happen never to have found anybody that is, I should give reasons why is that. Why is that? And it may not be because we think our rules are better. It may be because we are risk-averse in some way, but we don't know.

James Wagner: And the time constraint that we have. It makes us do this after the report, rather than before the report.

Amy Gutmann: Two things. One is that we do not know, and we do not know not for lack of previous bodies recommending, but maybe what we can do—maybe it is for lack of previous bodies saying, you know, one of our recommendations is: say what is stuck here. Given that you have promulgated this rule that says we will recognize equivalent protections, given that we hear that people would like some guidance on it, please give some guidance.

James Wagner: And presumably because part of our charge was to respond within a certain timeframe, we haven't invited a guest here from OHRP to talk to us.

Amy Gutmann: I don't think there's anybody who is right now authorized to give the response we want, frankly.

James Wagner: We trust that somebody will be after the report.

Amy Gutmann: That is what we are going to ask, that somebody be authorized to give us a response.

James Wagner: I think that horse is dead.

Amy Gutmann: No. It is a good – it's the right question.

James Wagner: The horns of the dilemma have been identified.

John Arras: Does anybody else want to pursue this question further?

Lonnie Ali: I just want to say we did consider there may be legal implications. We don't know. And who knows if the response hasn't changed over the course of a different administration, so there's something to consider.

Amy Gutmann: It's not targeting any, you know, the administrations and personnel that have changed.

Lonnie Ali: Exactly.

Amy Gutmann: It is that given our charge and the importance of this that comes up repeatedly, it would serve the government and the public well to have a response.

James Wagner: John, are you going to change course for us?

John Arras: I wanted to ask the subcommittee about the site selection issue a little bit further. So you divide up the territory into 2 parts. One part has to do with making sure that whatever site is selected, there is a research ethics infrastructure that can protect people. So that is the low lying fruit. That is the relatively easy part, and I think it is absolutely crucial that we insist upon that. But I do think that is the easy part. So because you could satisfy that criterion completely and still have concerns and worries about part 2, which is the responsiveness part, which as Christine put it, really doesn't have so much to do with protection of research subjects. It has rather to do with issues of justice, right? Now you recommend a kind of a research program here at the end of your ruminations on this issue, and I am still puzzling over exactly what kind of research you have in mind. So is it that you agree with the drift of all of these international guidelines that talk about the importance of responsiveness and how this is really a crucial criterion for ethical international research, but is it that you agree with that but that you have difficulty with different interpretations of what responsiveness would amount to, and that that is going to be the subject of research? So is it sort of like conceptual and ethical research you are calling for, or is it empirical work that you are calling for?

Christine Grady: I can speak for myself. I don't know that I can speak for Nelson and Lonnie about whether we agree with responsiveness. I would say the following: I think that the—my own view is that the notion of responsiveness makes sense to me in a way of thinking about minimizing the chances of exploiting places and people. However, the specification of how a study is responsive or not responsive and what that rules in and rules out I think has not been satisfying. So some of what I envision as the research agenda is that, sort of figuring out more clearly what does responsiveness mean, and what counts? What counts as responsive and what doesn't? Now there may be other—I think in thinking about it, sort of thinking about the recommendation would be even more broad than that, however, because there may be other notions beyond responsiveness that ought to be considered when somebody is selecting a site, and I think there are different ways to think about them. One possible way is to include them sort of conceptually under some kind of notion of responsiveness. So here is one that comes to my mind. When you have got long-standing collaborations and well-established infrastructure, there is a lot of value to continuing that long-standing collaboration and infrastructure. So that seems like important criteria. Is it different for responsiveness? Probably, but it doesn't necessarily have to be, I guess. Do either of you want to add anything to that?

Lonnie Ali: There was one thing that was mentioned this morning by Dr. Medford. I don't know he is still here or not. He made mention in his presentation that site selection is becoming increasingly more difficult.

[Crosstalk]

Dr. Medford this morning in his presentation made the comment that site selection is becoming increasingly more difficult because I guess as a private researcher, with the company he is with, there is always that competition to find the right site for the drug that they are trying to research, and they are in competition with other companies who are doing research on similar drugs, so we have that issue as well, of even though we talk about site selection and being responsive and all the ethical considerations that we go through, I think that is another caveat we need to look at that I did not know about before, is with regards to this issue of the difficulty of finding sites now. And he said more so internationally than you would actually think.

James Wagner: It's almost a competitive advantage concept, isn't it?

Nelson Michael: I think some of the issues we struggle with in terms of better defining responsiveness are that there can be really some nuanced thought processes about this. As an example, let's say you're in country X which is in the South of Africa, and it has an extremely sophisticated and a long-standing and durable tradition in doing research. It has attracted substantially diverse stakeholders and is a powerhouse for doing research. Maybe right next door you have a country that is coming up, and has similar health problems, but doesn't have the absorptive capacity for research that country X does. Is it meritorious, for the region, to have greater strength in terms of the intellectual strengthening, having research capacity? Is that good for the region to have some of those activities spread across more than a single country, and who makes that kind of decision? What is the thought process there? Is that meritorious or not, and who's to say that it is or isn't? So some of our concerns is to lay down what exactly defines the best in class responsiveness, it might be that in South America, you do research pretty much just in Brazil. Maybe in Africa, is just in the republic of South Africa. So I think there are other considerations, and the more granular we got on some of those criteria of what responsiveness could be, I think we could potentially not have thought about other consequences.

Amy Gutmann: Yeah. Responsiveness, as Christine and others have recognized, is a very broad term. It's not an ethical principle. Nobody—it is not an ethical principle to be just generally responsive. You know? It really needs—if it is going to become something that it would be through some of the other ethical principles that we have articulated, and my main concern about this part is that we identify—once we do identify what we think the research should focus on, that we make clear whether it is part of the protection of human subjects from harm or unethical treatment or if the category necessarily goes beyond that questions that I would call distributive justice as to whether research on human subjects is responding to the most urgent needs, whether they be health needs, or as Raju put it, other infrastructure needs and so on of the country, and there are some unintended consequences of some argument about responsiveness. So if you require research to be maximally responsive to the greatest health needs in a country, it may never happen, so it is a case where the imagined perfect drives out the actual good or if you don't

look at what research ethically is going to do and contribute to the infrastructure or other capacities of the country, it may minimize the good that ethically sound research does. So I think when we specify what we want research into this category be, we should be as specific as we can about what goals we are—what ethical goals we are targeting. They may be goals of distributive justice or expanded goals of ethical treatment of people beyond the subjects.

John Arras: Yeah. As I read these international guidelines and all of these codicils about responsiveness, and if I tried to create a theory to explain all of those, you're right Amy, it wouldn't have to do with the Kantian ethical principle of responsiveness, pure and simple. Right? But if I were to try and develop a theory, it would be that the drafters of those guidelines in some sense saw research as being nested, or the research enterprise as being nested within a larger project of global development. I think that that makes sense, so they are saying if you want to do research, it should further the health goals of the nation in which you are doing it. And then of course—and it is an interesting distinction that your group really needs to think about, is the distinction between health needs and just other kind of economic development needs, right? Because you could nest this within the theory of global development but have very broad notion of what development encompasses. Raju was making this point earlier. But as I read a lot of these documents, it seems to me that they have a fairly narrow notion of health, of responsiveness in mind, that it has to be responsive to the health needs of the local population, and that is something that is not like absolutely clear to a lot of people. It is debatable.

Nelson Michael: Just to clarify, would you believe that for our deliberations we should take the view that we concentrate on only health related responsiveness or that—should we somehow factor in non-health related issues with responsiveness? Is that becoming just too broad?

John Arras: I think that is what the debate is about, or at least part of it. I think that should be included in the larger analysis.

Christine Grady: I don't think it's just about that. I think Amy said it before, that some of the debate is about how are you responsive the health needs? Who defines what the needs are? Can you only be responsive if you are addressing the most important needs in the country? Who decides which are most important? There are a lot of details about that that are strictly related to just health needs, and I think the other thing that I just want to put out there—and I will just put it out there. In terms of the ethical salience of this notion of responsiveness, I think that responsiveness by itself, I agree with you maybe is not ethical requirement, that the idea I think initially was not only issues of justice, but avoiding exploitation. Now that is a controversial notion, too, in terms of what that means and how you do it, but that is—a lot of the groups that have put that in their guidelines have used it in that way.

John Arras: Yeah.

Amy Gutmann: Well let me just say there is an excellent literature on exploitation, and one position depends on whether you interpret exploitation broadly or narrowly. The more narrow you are, the more it overlaps with 'it's unethical', the more broadly you do it, if you get into—we had Dr. Medford who said 'we are absolutely committed to do ethical research'. Do we look to where we can do it for the lowest expense? Yes. And there is a broad notion of exploiting—that is

not—doesn't overlap with non-ethical treatment of subjects. It just basically, you find the least expensive place where you can do research ethically, and I think responsiveness is what we are, I think, thinking of recommending or not, is that we need more specificity into what the concerns that go beyond, don't disrespect, don't treat people unfairly or harm them. What goes beyond that? I think that is really—there are things that go beyond that, but they need to be specified if we are going to really be able in the future to move this discussion—more than this discussion, but any kind of rules and regulations.

James Wagner: Dan and John both on this point?

Daniel Sulmasy: I was going to say that Christine's response to John about the kind of research she thought was needed was more conceptual about what we mean by responsiveness is probably right, just based on the discussion we have had here, but it might help in our report to say at least what some of the questions would be that would be part of that research agenda, and I think you raised one that has come up on our own, that the testimony we've received, such as who represents the community or what we are doing, this other question that we have to face, which is sort of this presumption that we have that we are doing research in this developing country that is for the good of the country somehow, whether it is economic or on behalf of their health, and maybe it isn't. Maybe we have to be careful about whether or not they need microloans and shovels, if they need this, and balance that out. And 3rd, be careful about also the question of whether or not this is about our need not to be exploitative versus the actual needs of the nation when we are thinking about these questions, so all of these are very serious, and I think they deserve more conceptual analysis.

James Wagner: Very germane to this, actually, if I might—this would be a good place to insert a question, Christine Mitchell's question. There she is. She is talking. But she is the director of clinical ethics at—hi, Christine. But she echoes your comment and question in procedural ways. What method does the commission think or expect would be used to facilitate community engagement? How would the relevant community even be defined, notified, and educated about research protocols? What standing with the community's views actually have? Would they be merely advisory or could they veto? Who or what agency would ensure oversee community engagement, or does the commission just exhorting researchers to solicit and respect these inputs as a suggestion?

Nelson Michael: Those are all very good questions, so I will give you a vantage from my own field. I'm an HIV prevention researcher, and specifically we work with development of vaccines for HIV, and we work in Africa and in Southeast Asia. So in our field, the—I mean obviously UNAIDS and the AVAC were the agencies, were the organizations rather, that developed these guidelines. It's the second version. So in the execution of prevention research for HIV, these principles are deeply ingrained. Activists and other advocates actually sit on the advisory boards throughout the research community of funders in HIV. They are always on advisory boards. The community is deeply engaged in that sense. The community—and that is why I was emphasizing that engagement have to be done through the entire lifecycle so that you do not come to a community and present them essentially a finished product. They have to see that from the very beginning. If they're going to eat the sausage, they need to be involved in the first step of making it.

But that is a very idealized view of how it could work, but it is not so idealized that it could not be operationalized, because it is in HIV prevention research. Now the next question would be—and I think we had Larry Fori at—came to lecture to us within the past year and spoke pretty cogently about those issues. Now the next question should be how generalizable is that, and does the framework spread across other non-prevention, non-HIV prevention research, which is why we put in the caveat that Christine pointed out during our deliberations about just making sure we understood that this framework that we are describing is grounded in reality, but it may or may not generalize. So I hope that answers your questions.

James Wagner: The report will answer some of the how or at least make suggestions around the how question, in other words saying, “This needs to be done,” and I think all of these questions are how do we envision it being done in addition to what standing it would get to the community.

Nelson Michael: Right. And I think the how is to point to a very large field. HIV prevention research is a large and global and well-funded effort. I think that you could point to the fact that that field has developed a playbook that some of those plays may be generalizable to other activities, but to be—put a cautionary note on it that there may be implementation challenges with other fields, so we shouldn't assume that the plan as it is done in one field will easily transfer others.

James Wagner: We can offer it as an illustration.

Nelson Michael: Yes. We can offer that as an exemplar.

James Wagner: I think that is a great idea. I got John and Anita on my list.

John Arras: This is just a follow-up on Dan's really good questions. I think one question for the group here is, you know, I am just trying to get more specific now. One question would be whether research is intended to produce a product that would be distributed or disseminated the host country, right? So then Amy, forget about like optimal public health advantage. Just is it going to be made available period, right? Because two of the case studies that we looked at, the Haverix case and the Surfaxin case, were both cases where the manufacturer had zero interest, zero plans to make the drug available in the host country. Now for some people, this was okay, because the drugmaker was willing to contribute lots of other stuff, you know, infrastructure benefits. But in other cases, critics were very sharp in their condemnation, especially of the Surfaxin study. So that is one huge issue, right? What does it take to be responsive? And some people might say that a minimum requirement is that the drug you are working on needs to be available to the people from the host country, right? And Dan is I think really raising an interesting issue about exactly how much research does contribute to these places. If you do look at this within the context of a theory of global development, then this becomes a really live issue. Because if research is going to siphon off valuable time, energy, personnel from a local community, which has its hands full dealing with trying to treat people, you know, let alone do research, that could raise serious issues of distributive justice or exploitation as well.

Nelson Michael: I think you take it one step further, which is—and I will give you a tangible example. A year ago we began to work in Mozambique, and the Mozambicans have a

phenomenally small but really good group of MD and PhD immunologists that we have been working with to do HIV vaccine development. They were much further along than I thought they would be on our first few visits, but the cautionary note came from our sister agencies, the CDC and USAID, that were implementing the President's emergency plan for AIDS relief, and they used that same group to do things like quality control for viral load kits for resistance genotyping, for just the basic diagnosis of HIV infection, and their caution to us was, be careful that you do not overwhelm this group with a very sophisticated research agenda that all of a sudden we can't implement some critical prevention care and treatment services. So I think these are good cautions, and sometimes they actually don't need to spill out from the health sectors and nonhealth sector even within a single sector of that health field that you cannot implications that are unintended, which is why I come back to the issue of community engagement, because these discussions from the very beginning, from the first cogitation of whether or not a research activity should be contemplated, you have a broad range of stakeholders available. Those discussions can occur and adjustments can be made proximally so that you do not end up in trouble.

John Arras: Yeah. I like that, because what it suggests that the notion of community engagement can give is a kind of procedural way of defining—

Nelson Michael: Exactly.

John Arras: —proper site selection. I think that is really interesting. One of the more interesting quotes that I have seen on this issue was talking about site selection in places like Poland and the Soviet Union, that one beleaguered researcher said, “We are swimming in thrombolytics here.” Right? That is exactly—in other words, when a drug company comes in and does a lot of this research, they dump a lot of stuff in that area which may not have anything to do with their priorities.

Anita Allen: I just want to follow up on a lot of things that have already been said, but maybe from a somewhat different point of view. It seems to me that site selection question does impose a huge burden on the researchers to develop expertise which may not be at their fingertips. So you need to be a little bit of the political economist, public health expert, expert on community engagement, and of course you can always hire consultants and people to help you figure all of those things out, but it is not easy and straightforward. And I especially worry about the in some ways noble sounding development model, right? But if we know from the past, sometimes development has meant colonialism or something not so beautiful. It has often come with hegemonic assumptions.

I think we learned from the Guatemala incident that sometimes there are large-scale macroeconomic concerns that might lead researchers to collaborate with the foreign country to bring research there. Guatemala was a pretty vulnerable country that needed arguably US agribusiness down there, and so to keep the business but to also reap some benefit, maybe it looked pretty good to collaborate with the US Public health service on STD research. And I worry a lot about political regimes selling their people down the river, giving outsiders access to community groups that are going to say what they want them to say, not what they really feel and think. I worry about gender disparity in countries that might leave some subjects to agree to become subjects because their husbands or their fathers insist that they take part in the projects.

So I applaud everything that the commission has been thinking about. I would like to add, though, to the picture a bit more complexity as to what it really means to engage a foreign regime, the people in that regime, the people of all genders and that regime, the people of all classes of that regime, and to be real honest about the interest that governments may have in wanting outsiders to come in the first place.

Raju Kucherlapati: Though I want to be a little bit contrarian about this issue about responsiveness. Two points. One is a point that Amy made that responsiveness is not an ethical aspect, right? So first of all, this is an ethics commission, I do not understand as to why there is so much amount of emphasis on responsiveness. That is number 1. A second, more important aspect is that one of the most important criterion to be able to do a clinical trial in any country is that they've got to be patients in that particular condition in the country. And the fact that you are doing that trial or clinical study on that means that obviously there are people who are suffering from that condition and whatever you do is going to help them. That may not be the most important disease that they have. You may not be solving malaria in a 3rd world country or some other infectious disease or something, by you are indeed serving a need. So how could we say that certain kinds of clinical studies are not responsive? I would say every study, if you can get the patients—

James Wagner: Once you get beyond on phase 1 safety studies, because I do phase 1 studies.

Anita Allen: Right. What about a me-too drug for which there is already a pretty good intervention, and the drug company's patent is running out and they just want to do more research on another drug that could make them more money?

Raju Kucherlapati: How do you know? How do we know that? We do not know that.

Amy Gutmann: We have evidence about what happens when blood sugar goes down.

Raju Kucherlapati: But the examples of that, you know, there are larger numbers of statins for example, right? And yet other people have developed statins it turns out even me-too drugs that could be better, cheaper, whatever the case may be. So I do not think that we would be able to make it a judgment and be able to say, number 1, no other clinical studies should be done for me-too drugs, or you should be studying only for those diseases that are most important in that country. I don't think that is right.

Amy Gutmann: And nobody—just so we understand, nobody on the commission has suggested a recommendation of that kind, but the question on the table is whether it is worth recommending that the government supports some research that would narrow and specify the notion of responsiveness, which as John has pointed out, it is in many documents. There is this call as an ethical guideline, and I think we all agree that it is so broadly stated, and it is not a helpful ethical guideline, and the question is how—what in it besides our first recommendation, which is -never choose a site in which you cannot do—protect the subjects.

Raju Kucherlapati: But I'm going to maybe another point. Almost any side of the argument which you take, you can always find an example or two or three. The fact that you can find two

or three examples doesn't make it the norm, so we have to be careful in making too big a generalization about that.

James Wagner: I think if we do, as Amy suggested, always go back as far as we can to the fundamental ethical principles that would be underpinning what responsiveness means, for example, I think we will stay on safe ground. I really do. Nelson, last word?

Nelson Michael: I was going to say that just because trial participants in a country have access to a modality during a course of the study that might be meritorious and efficacious, in the absence of assurances that there will be access to the population at large after that study is done, could still make that study not intrinsically beneficial to all but a very, very small fraction of the citizenry of the country, so I would just put that caveat.

Amy Gutmann: I would just say that one of the other reasons why I think it is really important to have somebody outside of us, because we don't have the time nor do we have the charge to do this, but really become more specific, it is that everything that John and you said about responsiveness applies to many studies done in the United States, which are not then available to many segments of the US population, right? It does not just apply to international studies, so there is a lot more work to be done here. I'm going to let Jim—

James Gutmann: No. I'm just going to let you segue. I'm hoping, unless they are open questions, that Lonnie and Nelson and Christine have heard things that are going to help them in their particular charge. And I thank the commission for its engagement toward that end, to help them. And it is your turn.