



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT
Roundtable

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DR. GUTMANN:

We are going to make a seamless segue into a panel discussion so I'd ask everybody who has presented to come on up and I think we'll add perhaps a few seats to the table.

First of all, thank you all for joining us, and it's a great privilege for us to have you here to share your wisdom with us on a set of very thorny and important issues. So, we've made a practice of this, and you've got to trust us, it works, even though it's going to impose a discipline on you.

It's been very helpful for us to ask each of you if there were one, and only one, the single most important issue that you believe we as a Commission must address, or the single fact you believe that we must communicate about implementing federal standards in human protection research, what would that be? So one.

And I will begin with David and just work down, and then we're going to open it up to questions from the Commission members. Let me just tell you, we're going to take a break and then we're going to open it up for 45 minutes of public comments. So let's begin with David.

MR. BORASKY:

I was afraid you'd begin down here. I was not prepared for that question. You know, I would say informed consent reform.

DR. GUTMANN:

You could say just very briefly why.

MR. BORASKY:

Well, you know, in preparing to come here today, I talked with a lot of our researchers and a lot of our IRB members and asked them to identify what they saw as the top challenge for implementing the regulations both domestically and abroad, and that was always at the top of the list.

DR. GUTMANN:

Thank you. Sergio?

DR. LITEWKA:

Yeah, I was afraid to be the second right now. I'm here now. I think for all this discussion that evidently there is a divide that we have to put together between the moral foundations again of the regulations and the oversight and compliance of those.

So, trying to be brief, internationally speaking, I think that there should be more oversight, that's important. But not only more oversight, but trying to go away from what is just the formal issues and try to harmonize the same level of proficiency, if you wish, that you are

requesting for your researchers here in the States and IRBs to review for reviewing protocols.

DR. GUTMANN:

Thank you. Connie?

DR. CELUM:

So, I would stick with the point that I ended my presentation with about really looking carefully both at some of the specific guidelines around pregnant women, and I would extend that to breastfeeding women because I think in a lot of conversations, people focus on the pregnancy period. But for populations in the world where, for an example, Uganda with the fertility rate of seven, much of a woman's life she's not only pregnant, but she's breastfeeding for sometimes a year or longer.

And I guess my request is sort of two-fold, or recommendation would be. One is to look at the guidelines and see whether or not they are appropriate in terms of some of the specifics around paternal consent. And perhaps more clarity around when it's appropriate to move into the human populations for looking at safety.

And I think it's also important to look at harmonization, so that's not a regulation, but it's a practice and I think that perhaps because they have different requirements, OHRP and FDA I don't think always view the same guidelines in the same way and so it really requires tremendous efforts to navigate through those two very different perspectives.

DR. GUTMANN:

Thank you.

DR. FINS:

So I would follow what Dr. Wagner asked me in the last question. I would really try to broaden the discourse. I think whatever we do here is only going to be sustainable in between the Commissions if we have enough public engagement. And so, I think we really have to work on a longitudinal plan for science literacy, and I think we have a stem problem, you know, in science technology and math education. And I think bioethics can be a bridge between those domains. And we can teach kids science and make it interesting by teaching them bioethics at the same time. And it's a win, win and it creates a kind of glue that holds us all together, makes it sticky for the future.

DR. GUTMANN:

Very interesting, thank you.

DR. BAYER:

I wish it didn't sound like it being repetitive or hubris to say, I actually think that the distinct – reinvigorating the public conversation about the ethics of research in a way that distinguishes that from the importance of efficient and fair regulation would really be a huge step forward. I think they've been confused in ways that are very damaging.

DR. GUTMANN:

Thank you.

DR. LUMPKIN:

I was actually intrigued by one of the things that Joe said, and that is this issue of increasing within all of us that are involved in this enterprise the consciousness around ethics and what we do, and it's to this issue of ethics versus compliance. And I can give you a very concrete example of where it happened, and it's happened very effectively.

When Congress passed the law that increased the incentives for doing clinical trials in children, they addressed one half of the precipice that you were talking about earlier of this is a vulnerable population that people have not been going into.

They also mandated on FDA that we hire an ethicist because they said as this goes forward, we need to make sure we do this in an ethical manner. And we now have two fulltime card-carrying ethicists on our staff, for lack of a better term, who actually have integrated themselves into the process of what we do and who do get consulted, as Joe said, on things that simply has not happened in the past. And I think without their physical presence, which was mandated by Congress, that we wouldn't have this discourse going on within our institution and within our public advisory committees. Thank you.

DR. GUTMANN:

Thank you. Jerry?

DR. MENIKOFF:

I can actually say a great deal probably about the domestic system and issues that have been raised, but I think I will not. I think there's a fair amount of misinformation out there, but I guess I don't view that as the core part of what you're supposed to be getting at. I mean, I think there are two very, very different sets of issues that are being debated here.

On the international stuff, since that's the part of it you originally asked me to speak about, I think it would be useful if you actually did endorse or say that certain standards that are out there are in fact acceptable. That would be an important thing to do, and you certainly could do that.

DR. GUTMANN:

I just want to recognize Barbara because she had a question in earlier, so Barbara and then Jim. Go Barbara.

DR. ATKINSON:

I've been struck all day by this interesting dichotomy between the public good, public health and the individual and protecting the rights of the actual subject and the health of that. I actually think in a very misguided way, people in the Guatemalan study thought they were doing a study that might help the public in general with not enough care for the individual. So they were way over there.

And then I think of your babies. I've been thinking about them all day, the babies of the mothers who are pregnant, not to mention the pregnant mothers. And where do we set the line? And is that line moving and is that part of our problem right now, is deciding at what stage? I would say that yours would be one that the line has moved and at some point we need to make a decision that it's a public good, but it's also a personal good to those people, even though there's a risk of something to the baby, perhaps, or to something else. But maybe you can talk about where that line has moved or how it has?

DR. CELUM:

Well, I guess I would say that -- I guess I'm a pragmatic person, but when I try to imagine if I were on an IRB and I was reviewing a protocol for a product that had pretty minimal risk -- so I'll be very concrete here. So if we're looking at now these products, and there will be more to come, that have been in many cases FDA approved for treatment of people with HIV, but now we're trying to deliver them for prevention. And the question at hand is, are they safe, and eventually we really want to know, are they effective to help reduce the risk of HIV acquisition in a woman?

And I think it's very appropriate in that equation to weigh the risk. And if you're a woman in Western Kenya, as our colleagues have demonstrated, with a 13 percent risk of HIV acquisition, and we know that if she acquires HIV during pregnancy, she has a very high risk of transmitting it unless she's on treatment, my sense is that there's lip service to quantifying those risks, but that the real focus when the ethical committees are presented with these protocols is, well what do we know about the product?

And, I'm not sure that there's enough distinction made between even oral versus topical products where there's virtually no systemic absorption. So, I really do think that there needs to be more nuance, and maybe I'm not on an IRB, so maybe I'm totally misinformed. But I think that equation needs to be changed.

DR. GUTMANN:

Thank you. Jim has a question.

DR. WAGNER:

The first questions you asked when we went down the line was about the – to ask you to comment about implementation, what needed to be heard about implementing federal standards. And then Jerry comes down and says, “But there’s a benefit perhaps of holding up what is good about the standards.”

You know, the question itself presupposes that there is a certain adequacy to the federal standards. Now let me try to pose this as a yes/no question if I can, and I know you won’t be able to answer it that way, but let me try to pose it that way.

And that is as follows, do you believe that if one could pay attention to the harmonization issues, the contextual issues, the use of judgment and what not, that in fact the standards that exist are sufficient, if they were complied with, to give us an acceptable level of risk in human subject protection?

DR. GUTMANN:

Great question.

DR. WAGNER:

Do we have enough regs? We’ve just got to implement them better?

DR. GUTMANN:

I’m not going to ask all of you to answer it, but someone has to answer.

DR. WAGNER:

We could just have you raise your hand, yes or no. Okay, how many believe that to be true? Yeah, a couple of hands, yes. So it’s not about a matter of writing more regulation necessarily, it’s the implementation question. I think that’s important for us to hear.

And Ron had his hand up for both. Ron’s about to -- he’s wound up.

DR. BAYER:

The discourse around ethics is, there’s ethical and the opposite of that is unethical. So, to acknowledge that there are ethical questions or challenges in research that there may be a resolution to that is not exactly what you would’ve done, but that it’s not unethical, and that is different from what IRBs have to do where they have to make an up or down decision, would be a hugely important thing.

I mean, when the debate over 076 took place and people in South Africa who had spent their lives fighting Apartheid were told that they were unethical because they did a trial which they thought would be useful to South Africa. They said, "What do you mean unethical?" And so, I think

DR. LUMPKIN:

It's a context question.

DR. BAYER:

Yes.

DR. GUTMANN:

Raj?

DR. KUCHERLAPATI:

I want to ask a question which is a sort of a corollary to what Jim is asking, but one of the things that I have heard today starting from Christine and from many other people is that there is no consistency between the rules and regulations that we have, that the Common Rule and the rules that the FDA promulgates and the rules that international organizations promulgate have overlaps, but that they are not consistent.

So the question that I have, first of all, is it desirable to have a mechanism to, you know, bring all of them together into one set of rules and guidelines that would be applicable to everybody. And if we believe that that might be the case, how do we accomplish that?

DR. LUMPKIN:

I think there's something to be said for debating the question of whether it's good to be harmonious or in unity, whether you're talking about harmony or unity, because I think they're two different things.

I think we can be and we need to be harmonious on principles. I think we need to be on certain aspects of what we do so that we're not creating roadblocks that are just based on traditions, but I think we have to realize that we're not all clones of each other and we come out of different communities. We come out of different societies. We come out of legal backgrounds. There are other things that are playing into this than just the principles, so that when it comes to implementation, you will not find unity, you know, but you can still be harmonious in your adherence to principle and into your statements as to what you think the fundamental principles here are.

DR. GUTMANN:

Let me ask a follow up question to just, in some ways, both get more specific and also to raise an issue that I think has a lot of ethical

controversy about it and nobody spoke to directly, except Mack, and so I'll see what Mack has to say.

Mack, you said the issue of placebo control trials is placebos can be a part of well controlled trials, and that's certainly the case. But, you also suggested that that was the major ethical issue. So I see you nodding no, so that's good that you're nodding no.

So here's the question, which really involves almost all of the ethical issues that we've been talking about at the very high level. We know we've been asked to look at federal standards with regard to international as well as domestic. We know there are countries in which the best available treatment is not available for a variety of reasons, whether it be – it's always connected to economic development. It's also connected to the lack of adequate infrastructure. It's sometimes connected to cultural norms that don't – would predict that the populations won't use the best available treatment available in this country.

And there's been a huge amount of controversy about what, if doctors and scientists are looking for a treatment that will work in countries where the best available treatment is not available and if it were, it wouldn't work, what kind of trial is it ethically responsible to perform?

I look at Sergio because Sergio comes from, you know, a country which doesn't have all of the economic resources we have. And Mack, I don't know if you want to start, because I think I misunderstood what you first said because you presented it as, there's no rule. It almost sounded like you were saying there are no principles that could govern, standards that could govern whether we use placebo controlled trials or active or some other control.

DR. LUMPKIN:

No, no. Sure, no, to clarify, if that was the impression I gave, I clearly hoped that was not it, no. I think both within our regulations, within the E10 document, which is another IC document that talks about comparisons and the choice of comparators and when they are appropriate, is clearly in line with the 2008 Helsinki agreement.

So I think, you know, the issue that I was saying here is that I think that there are different ways that you can have an adequately controlled trial that will give you interpretable data at the end. And so, if I gave a different opinion, I do apologize. That was not the intent.

DR. GUTMANN:

Okay, I think it's important for the record that now I understand, and what you were saying is, there is no rule that would rightly tell you

always use placebo control or always use active, that you have to take other considerations into account.

DR. LUMPKIN:

Absolutely. And I think, you know, there are those who think the reason that we put the GCP in as our regulatory standard was because of this scientific debate about placebos with one of the previous versions of the Helsinki document.

And my point was, that was not the major element that went on there, that there was a whole host of other things. And in fact, I think our documents are actually quite, on the issue of choice of comparator, are actually quite compatible. Thanks.

DR. GUTMANN:

Okay, because I would just say that when you speak of well controlled trials, we should also keep in mind that there is a principle that is as close to universally recognized as any, which is do no harm. And that does guide you in what kind of control you would be using. It doesn't dictate it, but it certainly guides.

DR. LITEWKA:

Since you mention me, I think that there's always the common sense which applies. And again, you can't regulate common sense. You have to do what you think. There are to paradigms here in all the discussion from the last decade.

One was the 076 trial in Uganda. And then, you may say in that situation that the standard treatment was no treatment because it wasn't only the availability of the drug, but also all the infrastructure and all the system going around, so this is one thing.

The other is when you analyze the other paradigm, which was the Surfaxin studies in Peru when there was a drug available. And the reason for not accessing to that drug was simply that some particular families didn't have the resources to buy a very expensive drug, but you have that drug on the market actually, and the availability to administrate that product. So those are different situations.

DR. GUTMANN:

I just wanted to clarify that. Ron, did you have something?

DR. BAYER:

Yeah, imagine if what you said was –

DR. GUTMANN:

It would be easier for us to imagine if your light is on.

DR. BAYER:

Imagine if we said, "It would be better if we didn't have to use this comparator or use a placebo. But under these circumstances given X, Y or Z. The alternative is to disadvantage the population that might be benefited. That's a very different kind of statement.

There is a huge controversy over a trial that took place in Baltimore undertaken by the Kennedy Krieger Institute, which is devoted to the well being of children. And it was a trial of lead removal, lead abatement. Everyone knew what would be best, just remove all the paint, remove all the lead and -- but the cost was too high. The housing stock in Baltimore would've been basically abandoned.

And so, there was a trial where they did a little bit of abatement, a little more abatement, total abatement. And, one looks back on that and says, in America, how is it possible that we said we couldn't afford to do what was absolutely, clearly the best thing to do. And we didn't.

It was a very important piece of public health research. Was it evil? Very thoughtful people reviewed this. They weren't Nazi's, they were committed to the well being of poor kids. What does it mean that that trial took place under those circumstances with those resources available to those public health officials in that city?

That's the kind of -- if we could get people to talk that way, we would take a huge step forward.

DR. GUTMANN:

Thank you. Yes, Steve?

DR. HAUSER:

I've learned that if you look behind the microphone you can see if it's on. I have a question for David Borasky and maybe for some of the others as well. Importantly, this morning, you mentioned this regulatory hole that we have for some domestic research that is privately funded, exclusively carried out on international subjects and not as a prelude for data submission to the FDA.

And my question is, for particularly for early phase clinical trials, how large and important a problem do you think that this is?

DR. BORASKY:

So, you know, when I raised that notion, I think it was more to simply illuminate the fact that there is this hole in the regulations. I don't know that there's data out there and how much research actually gets conducted in that window, but I find it odd that we have a system that protects a good chunk of things, but it's decided that this piece of it, we'll just leave it alone.

And it seems like it's an unnecessary gap in the coverage of research that could be closed, much as it is I would say in the animal research world. But, we don't have a systematic blanket coverage for everything. There are these gaps.

And it certainly provides the opportunity for unethical research to happen with no oversight. There are certainly a small number of anecdotal stories about it happening, you know, studies of facelift operations that were done in a private practice where half of a face was done with one method and half with another. And at the time there were complaints made somebody said, "Well, that's not federally funded or FDA regulated, so we're not going to be able to do anything about that."

To me, the main point was that we have these gaps in our regulations and it seems like this is an ideal time to tighten those up and decide that if we're going to protect people in research, why wouldn't we do that for everybody and not simply tie it to who's paying for it?

DR. GUTMANN:

Thank you. John?

DR. ARRAS:

Okay. I've been doing some reading on the off-shoring of biomedical research, not so much NIH, but pharmaceutical companies. And I've been puzzled by something that I'd like you all, or some of you to respond to.

Most of the international documents that we look at talk about the need for research to be responsive to the health needs of the country, okay? If you look at CIOMS, if you look at all these, Helsinki, all these regulations say that in order to be ethical, research must be responsive to the needs of those countries.

It seems to me that when pharmaceutical companies lately are farming out their research to contract research organizations in Eastern Europe, in all sorts of South American and Asian countries, in order to eventually get FDA approval here, precisely what they are doing is to do studies overseas in places where there's zero intention to market their drugs or to really benefit the local population beyond doing the actual study.

So I'm wondering what you all think of this? I mean, to me, this is a real puzzle, right, because if you look at the disparity between practice and norms, it's just an enormous gap.

DR. GUTMANN:

Who would like to take that? David?

DR. BORASKY:

Well, you know, I think I'd just – my main comment would be to say that I don't think, it's not entirely fair just to hold industry sponsored research to that norm. It's certainly, post trial access is a huge concern in say, HIV prevention research. Often there are no hard guarantees in place that if this microbicide works, it's going to be rolled out quickly. And even when something like circumcision works, it's rolled out unevenly. You know, I think that's a real challenge.

I think your question goes more towards the justice, and maybe the questions about who says it's okay to do research in this certain geography as their role of regulators to step in on that or is to just to the ethicists? But I don't think it's entirely fair just to put the spotlight on industry sponsored research, even though there's certainly a lot of – in the popular press – a lot of concerns about trials being done whether it's in India, China, Eastern Europe.

DR. LITEWKA:

In the case of Latin America, at least what I know, most of the clinical trials carried about by pharmaceuticals are phase two, three, and four. You can question another aspect which is the post-marketing trial, which is another thing.

Now, you have to consider that many country have different epidemiological characteristics in the same country. You have in countries like Argentina or Uruguay or Brazil, pathologies which are from very developing countries and chronic pathologies which are more for other sort of countries, so eventually if you are testing a hypertensive drug or oncological drugs, eventually it will reach the population.

DR. GUTMANN:

Mack, did you want to say something on this?

DR. WAGNER:

Connie had a comment too.

DR. LUMPKIN:

Just real quickly. I mean, I'll be the last person to ever speak for the pharmaceutical industry, and I'm sure I'm the last one they would ever want to speak for them.

But, and obviously it's a question that really should go to them. But, I'd be interested as you guys debate this issue, I mean, some of the things that I've heard back and forth are, you say that it has to accrue to the benefit of the local population. And the question is, how do you define benefit there? Can you only define it in terms of having access to the product after the fact? Or from an ethical perspective, can you argue benefit in the sense of money being spent to further build up the medical infrastructure, money going into the area that there are benefits perhaps from this enterprise to the local community other than having access at the end of the day?

Whether that's a valid argument in the world that you all live in and the ethical world that needs to judge these I think would be a very interesting playback from what Dr. Arras had asked.

DR. GUTMANN:

Connie and then John?

DR. CELUM:

So, just I guess one dimension to the post trial access question that I'm beginning to puzzle over is, I've always thought of it as for study participants. Basically you write in the consent if this works, we will give X amount of this effective intervention to either the placebo arm or to both and so on and so forth.

So I think that one dimension that's entering into the discussion now for as we start having hopes that new ARV's may offer protection is really the balance between -- should the focus be on study participants? Should we do that in a more efficient way, you know, basically really just giving the drug and put more effort into demonstration projects?

I mean, really if your goal at the end of all this is to get things into the population, then maybe more resources should be put into demonstration projects. But I think that discussion is just beginning to happen in terms of what is the right approach to that.

DR. FINS:

Just to add to what Mack said, I think another way to kind of redistribute some of the resources that would go back to the communities that actually served as the infrastructure for the research is through looking at Bayh-Dole, the Bayh-Dole Act, intellectual property and royalties. A

certain percentage of royalties could be redistributed back to the population that led to the profits in the first place.

I mean, people have been talking about revisiting Bayh-Dole for 30 years now, and I think it might be right to add these concerns to that process.

DR. GUTMANN:

Nita.

DR. FARAHANY:

I wanted to return to Jerry, your comments about endorsement of existing regulations. And to ask you a bit about what you meant by that and if you could elaborate a bit. So some of the questions I have, and this is really open to other people as well, if you have ones that you think we should be endorsing, which ones would you in particular recognize and say that we should endorse? And what would endorsement mean? Is it simply a seal of approval or is it doing something like Joe suggested which is creating educational programs and trying to contextualize and show the ethical components of it and what it means?

Do these different things that you may suggest need to be better defined? So, Christine earlier talked about equivalent protections, and she thinks that that's an important one for us to endorse, but also to define and give practical meat to in order for it to actually be effective.

And then finally, would endorsement require international cooperation and buy-in for there to be legitimacy around the different international norms or standards. And if so, how do you think that we would go about that? So that's about five different questions and one for you.

DR. MENIKOFF:

Okay. No, they're great questions. I guess the starting point for my comment was that I'm not sure there actually is much difference between all of these various sets of rules. And a lot of what it comes down to are the fine points that seems to be what a lot of the debate was about.

I mean, as a U.S. regulator, we have certainly been sending the message for quite some time that it's not just about compliance, that what really matters ultimately are the underlying ethical principles.

And the other part of the picture is as others have noted, there's actually a lack of empirical evidence on how much benefit we are getting in terms of increased protection to research subjects from all of the various steps that we have in the current system, whether it's IRB review, or it's education of researchers, etc., etc.

So, given all of that, it makes it sort of difficult to say that this particular

system, whether it's the U.S. regs or ICH E6 or GCP, one or the other is better. And again, thematically, they're all pretty similar. I mean, you got some IRB review. You have some requirement in terms of informed consent. And I might add, as what I view as an important aside, I think to the extent there are problems with the system throughout the world, informed consent is the one area that there is need to do better. And in fact, there are actually fairly straightforward ways to improve informed consent. But –

DR. GUTMANN:

Do you want to give us one straightforward way of improving informed consent?

DR. MENIKOFF:

Okay, and I know a lot of people object to this, but a lot of the debate out there is about process versus form. And a lot of people bad mouth consent forms. And yet, if you look at the examples out there, and there are quite a few of them, of scenarios in which the front pages of the New York Times is discussing a study that had huge problems -- the Avandia study, which got mind boggling amounts of press, is a great example.

Take a look at that consent form. It has like, one sentence about, about well, we're not sure whether this drug might increase your risk of heart attacks. When there were front page New England Journal studies about this from the leading cardiologist in the country, editorials in the New England Journal, debates by FDA regulatory bodies in the 12 or 15 however many page consent form. You couldn't have had one big paragraph, maybe 10 sentences on the front page saying, "Look, the leading cardiologist in the country reevaluated the data put out by the company itself, which wasn't particularly eager to put it out, and he concluded you're going to have a 50 percent increase in your risk of getting a heart attack if you're on this drug when there's an equally good drug out there."

Why aren't we debating that sort of thing, that there are very straightforward ways? We use paper with clear language to convey information all the time.

DR. GUTMANN:

But Jerry, is there any debate about that? I mean, they didn't do what they should've done, right?

DR. MENIKOFF:

Okay, the issue is that an outlier? And I'm not sure under the current regulatory standards that is that much of an outlier.

DR. GUTMANN:

So you are saying that under current regulatory standards, what Avandia did was not against the regulations?

DR. MENIKOFF:

It is unclear to me, and the FDA could comment –

DR. LUMPKIN:

No, I can't.

[Laughter]

DR. MENIKOFF:

You have vague regulations. A lot of discussion here has been about the fact that regulators sort of over-regulate. And I'm just pointing out in some areas, the regulations actually in terms of informed consent are very, very vague. So what you now end up with – and this is a theme that was noted earlier – that how much of a problem is due to what the regulators are doing?

When you have 15, 20, 25 page consent forms with the salient five pieces of information that somebody should know, let's go back to ethical principles and the Nuremberg Code. It talked about somebody making an enlightening decision on whether or not to be in this study.

How many times have you seen a consent form that actually says on the front page, "By the way, here are the things you should think about in deciding not to be in a study." And I have had IRB members who respond to me and say, "Wow, that's a new idea. The consent form is actually designed to help you make a decision as opposed to giving you a bunch of information that you need before we could allow you to be in the study."

DR. GUTMANN:

Yeah, that's actually very helpful. We have had other – there is a convergence here of a view that with all of the details in informed consent forms, there is no – and we need to check this – but there is no obvious requirement to just put the most important risks as well as benefits up front in language that is as simple as the language could be without being misleading.

DR. MENIKOFF:

And that would be a huge benefit if you just made changes like that. You know, whether or not you could just mandate that under the current regulations, that might be an issue.

DR. SULMASY:

I was going to follow up again on this question about what's driving all the research going off shore. I mean, the statistics were pretty impressive. And I mean, it has to be that it's cheaper, right? It has to be. And yet, the pushback that we heard before is, the regulations are exactly the same. They have to comply with all these regulations.

So, what's the difference if the regulations are exactly the same, or we've got the same rules? Is it the way those rules are implemented in these countries? Is it, it's cheaper to recruit people because they've got, you know, five bucks there will go a longer way? Is it a combination of all of these? What are the things that are behind it?

DR. LITEWKA:

Well, there are two different -- if the research is funded by the NIH indeed there is an interest in collaborative research, so there's another. When you talk about pharmaceutical research, the reasons based on the advertising that the CROs have an internet and are available everywhere.

It's not about the regulatory issues. Actually, the CROs say that the regulatory issues are great. But you have a large pool of population. Those are treatment naïve. Normally those are the other reason.

In many countries like in Latin America and Eastern Europe, you have lots of medical facilities in which you can perform research. You have lots of trained physicians and investigators which salaries are much lower than the average salary of the U.S. investigator.

And maybe, maybe, I'm not very sure, maybe there are shortcuts that you can take and make the research easier, but I can't be positive about that, but it could be a reason. When I say shortcuts, I'm not saying that deliberately you have less regulations, but maybe it's easier to overcome the burden of the local regulations, but those are some of the reasons, and it's cheaper for all of those reasons.

DR. CELUM:

I want to challenge that it necessarily is cheaper. I mean, I've had to go really advocate hard with some of our funders about who I think did think it would be cheaper and were a little bit surprised at the budgets. But, if you're actually going to do this in a collaborative way, you build facilities and such.

And just to go on a little bit, I mean, for the same study that we did in Seattle, the first [unclear] study where we enrolled, I forget, something around 300 participants, but some of the international sites had maybe four or 500. Their staffing was much higher even though the staffing cost per person are lower. But, you literally have to do it all.

And I think that a lot of times there's a tradeoff in that some of the research done in U.S. institutions are done in research centers where you, probably don't want to be quoted here, but that there is some ability to subsidize research when one study's going away and another one's started, whereas in many – I'm really speaking now with Africa at the front of my mind – these are standalone centers. And you have to pay every salary there. And so, that doesn't translate to cheaper costs. But maybe you're really asking more about pharma and not sort of the NIH model for research.

DR. SULMASY:

I think I just wanted to say that there is a big distinction I think between NIH research and pharmaceutical research probably on this topic, unless the FDA wants to say differently.

DR. GUTMANN:

I want to ask, I know there are some members of the public who might have questions for panelists. I wanted to see if Francis Kamm, who's a bioethicist, do you have anything you would like to say? Come on up if you do. Okay.

DR. KAMM:

Well, one thing that struck me –

DR. GUTMANN:

But come to the microphone though, if you would, please?

DR. KAMM:

I think it was Mack – you said that our perspective on things might be different than the perspective elsewhere. And you used the term perspective, and I thought part of what Dr. Gutmann brought up was relevant. It might be that the conditions are different elsewhere, so that, you know, whether someone will be worse off if you use placebo or not, will be different than in the U.S. But the perspective that we use wouldn't necessarily be different because if in the United States there was an area, for example, where people wouldn't take a certain sort of medicine so that they would not be worse off if you omitted treatment, the perspective would be the same. It's just that the fact of the matter is that you wouldn't be harming someone in virtue of the facts in the case. So you could maintain the same perspective internationally. You wouldn't have to say, "Well, you know, in this country, they don't care about human beings, you know, as much as we do."

So, it's important not to use the word, I think, perspective. Rather the facts or the conditions or the context are different.

There was one other thing I wanted to come back to and that's the importance about what I think you were focusing on, namely the question of the research subject versus the benefit to the population in general. And Dr. Gutmann tried to deal with this. It's a very difficult issue and I admire her tenacity in trying to get –

I mean, even if you hold constant whether you're letting a patient die. For example, suppose you wouldn't give standard of care to someone in a treatment, in a research experiment, right? You would omit to do that, and perhaps it would be wrong to do that.

In this context, where you omit treatment and you don't help someone live, you're not actually killing them, you're not harming them, you're just letting them die or something. If you're doing it in order to gain information as they did in Tuskegee, for example, in order to help a population, it's true that even though you're letting them die and not killing them, and you would be omitting to develop a treatment as a consequence of which a lot of people in the general population would die, still it seems to me – and I think many philosophers have argued – that there's a difference between these two letting dies. Because in one case, you're deliberately using someone to acquire information that will help others, as opposed to simply not treating people because you're busy treating somebody else.

So, for example, if I omit to treat one person in order to go and save five people instead, it's also a question of either, you know, letting this person die or letting those five people die. But there isn't a certain type of use of a person, you know, omitting what they're entitled to for the sake of acquiring information to help others.

This is just one example I wanted to say of how subtleties here can matter, and why ethics education matters. Getting people to think about cases – you don't have to do high level Hegelian or Kantian theory. You can just get people – I don't know if I've done it successfully here because I wasn't prepared for the question. I appreciate the opportunity very much.

But, if you get people to think about cases, you know, and say, "Look, there is this difference," that will heighten their ability to deal with the subtleties of ethics and not just regulations. Thank you. I hope I haven't taken too much time.

DR. GUTMANN:
No, thank you. Thank you.

MS. ALI:
[UNINTEL – OFF MIC]

DR. KAMM:
No, I was trying to show that at least intuitively we think that saving the five rather than the one might be permissible. It's a triage or scarcity of resources. But, that it would be wrong to let someone die merely to acquire information in order to help others. At least it's prima facie wrong, okay?

That was the point, to point out that even though as was said correctly, it's not a killing, right? It still could be wrong and there are so many subtleties that this is one of the reasons that ethical sensitivity that can be developed by considering these cases, right, is so important.

DR. GUTMANN:
Another subtlety is that when bureaucratic regulations prevent somebody who wants to help save a person, it's not the same as helping some people instead of others. It's putting unnecessary blockages in front of a human will to do good, and that's worse than simply deciding you're going to help people in Latin America versus people in Africa. So there are conscious decisions being made. Barbara? I think we've got an important conversation going.

DR. ATKINSON:
That's really true, and this relates to this too. My issue was really that it seems to me that times have changed and we need to continue the ethics discussion on this because what might have been 50 years ago more acceptable, not acceptable, but more acceptable has changed to now too and we need to keep pushing at what the real issue is, where that borderline happens, because I think it's a cultural issue and it's an understanding of ethics that changes over time.

DR. GUTMANN:
Joe.

DR. FINS:
In response to Frances' comments, I think one of the things that we should try to maybe build into the process is regs are uni-dimesnional, they're on a piece of paper. They really don't speak for themselves. And sometimes, there's a role conflict and there's role sequestration issues where some people, if you're running an intensive care unit, you have an obligation to the unit, but not to the individual patient, which is a fiduciary obligation, which is not transferable if you're a physician to that individual patient.

So, you know, having the investigator and the clinician and others in a

kind of conversation about balancing engenders process that otherwise may not occur because there might be multiple goods that you're trying to achieve. They may be incompatible with each other, but when you think about regs, I think we have to build a third dimension of populating it with roles and responsibilities.

DR. BAYER:

I've been puzzling over the issue of the moral obligation to do research in communities where only that community, at least potentially, can benefit. I think there's actually a challenge here for the Commission.

We say that over and over again and we say that it's unethical to do research in a community or among people that will in no way benefit directly from doing the research. I actually think that there's a challenge for the Commission to address this issue.

Why is it okay to have people in Indonesia make our jeans that they can't afford to buy? Why is it okay for us to hire workers to build buildings that they will never be able to afford and if they're paid a fair wage?

There's a difference, it seems to me, between exploitation and unfairness. And the question of whether a community can benefit in some ways that have nothing to do with the medical intervention by research taking place there is separate, it seems to me, from the issue of whether they have been subject to kind of prima facie unethical exploitation or unfairness.

It may be that it is wrong to do it, that it is wrong to do research in a community that can not benefit. And not all research involves life and death and not all research involves dangerous interventions. But I think if you could clarify why it is, if you think it is, obligatory to make the research relevant to the community within which it's doing, you will really advance the conversation that I think has sort of been frozen in a kind of almost knee jerk kind of standard that I think we haven't really explored carefully in a long time.

DR. GUTMANN:

Before we break, we have five minutes. Is there anybody in the audience who would like to pose a question to one of our panelists? We'll then take a 15 minute break and reconvene for public comments – specifically for the panelists? Good, go ahead.

AUDIENCE MEMBER:

Hi, I'm Maya from the Lancet Medical Journal, the North American editor.

DR. GUTMANN:

Yes?

MAYA:

Yes, so I have I guess two issues, and maybe one of you can answer it. But, we're all talking about existing research and how to mostly protect subjects, but I think at the beginning of the process, the question that I am a little bit more concerned is the responsibility of who is actually asking the right clinical question that needs an answer? And that actually will then define usage of human subjects worldwide or domestically.

So we don't have a standardization of who has the responsibility to ask the right questions in order to, you know, avoid human redundancy and financial redundancy. So that's one issue, I think.

DR. GUTMANN:

So is it the issue of scientific validity of the study, what's called scientific validity in that it has to have –

MAYA:

Well, it's really which clinically unmet needs are we trying to solve in order to actually have human subjects being used in the research? So that's one.

And the other one is kind of related which is the funding part of a clinically unmet need. A lot of funding bodies, I think including the government versus industry don't actually require systematic reviews and meta analysis of a question in order to actually justify further research. So that is something I would like to have standardized, okay.

DR. GUTMANN: Joe, would you start? We're going to take a break and come back at four o'clock because I'm just watching the time here. So Joe?

DR. FINS:

Just briefly for the first part of the question, there's a lot of discussion about the importance of registries and there is clinicaltrials.gov for NIH sanctioned trials, but that's something that needs to be expanded more widely and I recently wrote a paper about this in JAMA about DBS trials, deep brain stimulation trials having a registry with Thomas Schlaepfer. And it's important also, and we talk about registries, and we talk about negative and positive results so that people can be informed about this.

And sometimes, industry tries to sequester the negative result so that other competitors go down that same cul de sac. And of course, that's unethical.

DR. GRADY:

I guess I wanted to just clarify what Maya said a little bit further. It seems to me what you're suggesting is that in order to do ethical research, we need to know what we already know and what we don't know. And then, make some judgments about what's valuable to ask. And so, part of your question was who should do that? And I think that's a harder question.

MAYA:

Who's the responsibility because the public is nothing to do and there's some –

DR. GRADY:

So maybe it should be public priority setting on research agendas or something?

DR. GUTMANN:

Joe's answer goes somewhere towards that which is a responsibility to publish negative as well as positive results so we know what's been done.

I just want to thank our panelists so very much for a very enlightening set of – thank you. We will reconvene promptly at 4:00. Thank you all.