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for the Study of Bioethical Issues

TRANSCRIPT

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DR. GUTMANN: I am going to get started because we have a wonderful guest.

Please take seats.

Our next session will focus on national-level review of certain types of pediatric research. Initially contemplated in the late 1970s by one of our predecessor bioethics commissions, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, this type of national-level review is also codified in federal regulations.

Dr. David Wendler -- welcome -- is the head of the Unit on Vulnerable Populations in the Department of Bioethics at the NIH Clinical Center. Dr. Wendler has served as a consultant to numerous organizations, including the Council of International Organizations of Medical Sciences, CIOMS; the American College of Cardiology, and the National Institute of Aging.

His current work focuses on the ethics of research with individuals who are unable to give informed consent, very relevant to our work.

Welcome.

DR. WENDLER: Thank you.

So, basically, what I am going to try to do is just provide the members with a kind of framework on the basics of Category 407 that, hopefully, will facilitate the discussion that we might, hopefully, have after my talk and, then, as part of the roundtable.

So, just a reminder, I work for the federal government, but these are my own views, not anybody else's.

David Resnik went through some of this background. So, I probably don't

have to repeat it.

These are the four categories of pediatric research in the U.S. Federal Regulations, 407. The one I am going to talk about is the fourth one.

One thing, just to remind people, typically, people think about 407 with respect to research studies in children that don't satisfy the risk limits on 404, 405, or 406. That is right, but it is not limited to that. 407 is research that is not otherwise approvable, and that covers any other reason why it might not be approvable, although I take it for the most part the relevance here is, as I have it, more-than-minimal risk. So, it is more than and, also, it doesn't satisfy 404. It does not offer the prospect of direct benefit, so it can't be approved in 405. And it is, presumably, going to be done in healthy children. So, it can't be approved in 406.

And one of the lessons I want to just remind people, I think about 88 percent of all academic debates really involve people who don't disagree on the content; they just don't recognize that they are using their terms in different ways. And I think that happens a lot in this context, particularly, as you have seen this morning and earlier, with respect to what constitutes minimal risk. So, I think it is really important to be clear on the terms before we try to have a really substantive discussion about these things.

So, here, basically, are the requirements that have to be met before a study can be approved in 407. The penultimate bullet, just to highlight, has to be consistent with sound ethical principles. Obviously, that is extraordinarily important. Figuring out how to satisfy that requirement isn't always entirely clear.

And the last thing to note -- I think David Resnik hinted at this this

morning -- there is no explicit limit on risk level for 407. Some people think there is. And if you read the National Commission that Dr. Gutmann cited, I think it is actually unclear whether or not they think there should be such a limit. So, we can talk about that if we have time. But at least explicitly in the regulations, there is nothing about a risk limit.

So, here are the questions, I think, or at least some of the central ones: is a minor increased risk acceptable in healthy children? It can be done in children with a condition under 406, but can it be done in healthy children? If so, how do you define it; how do you implement whatever that standard is going to be?

Are there cases in which even greater than minimal risk -- so, John this morning talked about a minor increase over a minor increase, would that ever be acceptable research? How the heck would you define that?

And then, apart from risk limits, potential benefit, what other requirements might be put in place to make sure that the research is consistent with sound ethical principles.

So, those are the basic, I think the most important questions, or at least the ones I am going to focus on here.

So, one of the things to get really clear on, again, is to try to figure out exactly what minimal risk means and what more-than-minimal risk means. I think a lot of people assume, and I think this is a mistake, that the distinction between minimal risk and more-than-minimal risk research is the distinction between research that poses no chance of serious harm and research that poses some chance of serious harm.

In fact, if you read through the National Commission, Paul Ramsey has

this wonderful bit where he talks about the fact that he thinks the National Commission is assuming minimal risk research. "Oh, it is not a problem because they are assuming it doesn't pose serious risk."

And then, later on, they will say, "But we have to have really good insurance for kids who experience serious harms as a result of this research." Somehow people aren't putting those two together. So, that is not the right distinction, and that is clear.

David gave the definition this morning. At least explicitly, the way the definition is written, it is "risks ordinarily encountered in daily life". Clearly, children face some risks of serious harm, including death, during activities of daily life.

So, what is the difference? And this, I think, is the question about why you guys have been struggling with this so much. Basically, what are you trying to do when you decide a study is minimal risk? Basically, what you are trying to do is you have some threshold for what is minimal risk, and what you are trying to ask is, is this particular study, so is this study of a vaccine for anthrax, are the risks of that study less than or greater than whatever this threshold is?

Well, to answer that question, you need to know two things at least. You need to know what the threshold is, and you need to know what the risks of the study are.

I think there is at least some -- David hinted at this this morning -- some agreement on the threshold, but we are still working on that. And then, oftentimes, you don't have really good data on what actually the risks of the vaccine are. So, it is hard to make these considerations, but I think it is at least important to try to be clear about how you

do it.

So, here are some of the different accounts:

The risks of daily life, that is the federal definition. As David pointed out this morning, it doesn't say whose daily life. So, people have talked about that. The IOM Committee thought it is the ordinary, average children. Some other people, Lainie Ross and Skip Nelson, who I think talked to the Committee previously, endorse what a prudent parent would allow.

What I think is important, whatever of these standards you prefer, I think the important thing to recognize is we are talking here about research that doesn't offer at least direct benefits to the subjects.

So, what I like to think about this, I think it is helpful to think about it in terms of some kind of charitable activity. Basically, what we are asking in this context, when is it acceptable to have children be in an activity that is designed to benefit others and poses risk to them?

And I think there are, if you think about it, in daily life there are activities where we have children face risks in activities that are designed to benefit others. So, I think keeping that frame in mind is really important here.

So, basically, this is the way I think about it: what are minimal risks? Minimal risks are the risks of activities, common-occurring activities, for children which are designed to benefit others, but we think they are acceptable. I think that is basically a way to think about minimal risk.

What would minor increase over minimal risk be? Well, I think, basically,

what they are -- and this is in a paper I have referenced here -- that basically would be activities which aren't common, aren't ordinary; we don't allow all the time, but we allow sometimes in some exceptional cases for some children, even though the risks are slightly higher and they are designed to benefit other people. So, that is at least one way to think about these two thresholds.

So, the first thing, as was mentioned this morning, I think a lot of times people have different definitions of minimal risk. They think the data are different. They don't agree on the data. So, they are not really agreeing on what they are talking about in the first place.

So, I think the first question to ask is whether or not these studies really do pose more than minimal risk. Anecdotally, I know a lot of times IRBs I have worked on over the last 17 years, people think things are minimal risk that aren't really greater-than-minimal risk.

So, this is a paper I did with Sumeeta Varma, who is a fellow in our Department, about eight years ago. We looked at all the studies we could get data on at the time that had gone through the 407 process. These are studies where the IRB said it was more than minimal risk. The expert panel agreed it was more than minimal risk. And I think in every case but one it was clear that those studies really posed minimal risk. So, the first thing you have got to be clear on is whether these studies really are minimal risk or greater than minimal risk.

So, roughly, just to give you a sense, we have tried to come up with some data that David mentioned this morning on, if you take this data seriously, what does it give

you in terms of numbers? So, this is a very rough approximation of the kinds of risks that would meet that minimal risk standard.

And so, again, what you need, I think, is you need a very systematic way of finding out as best you can what the risks of the study are and comparing them to these risks, if you want to make this judgment in a more objective way, rather than just based on intuition.

So, the first question, is minor increase over minimal risk allowable? Well, we allow it in 406 with children who have the condition under study. My sense is I can't see any reason why you should think it is acceptable to pose greater risks to children who have the concern under study than children who are healthy.

So, take a complete different example, like building houses for the homeless. It would strike me as very odd to say, well, children who are themselves homeless, they can face really high risks or higher risks in this activity than children who have homes. The fact that you have the concern doesn't seem a reason to pose greater risk to you. Maybe, if anything, it is a reason to give you more protections. If that is right, then it suggested a minor increase over minimal risk should be acceptable as well in healthy children.

This is something that was also mentioned this morning. The U.S. regulations don't include a necessity requirement. They don't say you have to do parents first, adults first, older children first. So, I think that would be a really important thing to have if you are doing this sort of research.

How about risks that are greater than that? Well, I think there are at least

two cases in which you might accept more than a minor increase over minimal risk.

The first thing is, remember, we are worried about this kind of research because children aren't competent. But there is actually fairly-decent empirical data which suggests that at least some older children can really understand the research in question. So, I think that suggests that, at least if you limit a study to those children, you might be able to justify something like John's standard of a minor increase over a minor increase over minimal risk. So, that would be exception one. I think in that case it would be acceptable that children understand it and they agree to participate. Maybe slightly greater risks would be acceptable.

The second one is direct benefits not defined in the regulations, but the other categories are limited to, 405 is limited to prospect of direct benefit. Some people have recognized there may be cases where a study offers some non-direct benefits which could justify a study.

One example was a study for G-CSF in bone marrow transplant -- this was an actual 407 -- where the panel said, "This doesn't offer direct benefit, but it offers children the chance to help their siblings. This is an important benefit that could justify the risk." That is one possibility.

Another one we could talk about more, if you want, I think in certain cases just contributing to valuable studies can add benefit to children's lives, and that in some cases can justify somewhat greater risks. So, level of contribution is going to depend upon how much they understand and the value of the study.

There is obvious potential for abuse. So, we want to make sure that this is

done in the right way. So, I think this is a good reason to only allow these cases for a 407 panel, not for individual IRBs.

The last thing, I will just say a couple of other safeguards you might consider in this case. One is just we are looking at risk/benefit for populations. Whether or not that is true of an individual in that population is not always clear. So, one thing you might say is we want individual evaluations for the specific children that we are going to enroll.

Another thing that was mentioned this morning, it is really important that parents understand these studies. There are ways to try to do that.

Also, if you are basing your justification for more risk on the fact that children understand, then I think there should also be some evaluation of whether that is, in fact, the case for individual children.

I don't have much to say about this right now, but I think subject selection in these studies is going to be extraordinarily important. Even if you get everything right, it is going to be really important what processes you use to decide. You guys discussed this a little bit this morning about who is going to be in the studies and who is not going to be in the studies, both the reality, but also I think the importance of focusing on and taking advantage of specific groups would be really problematic.

The last thing, I think you could have monitoring in this case. Typically, we don't do this in clinical research, but you could have independent monitors, if it is a longitudinal study, to make sure that it continues to make sense for individual children; they continue to agree to participate, and the risks don't become excessive over time for them.

So, I will stop there. I had some things on wording from the National Commission, but I think maybe we will just wait in case people want to talk about that during the question-and-answer.

Thanks.

DR. GUTMANN: Thank you very much. You really covered a lot of territory.

Questions? Dan?

DR. SULMASY: Thanks, David. That was very helpful.

I wonder if we just did a step back and think about the children as a specific case of the category of a vulnerable group, and whether it matters in the moral analysis that the study that is being proposed is designed to benefit members of the very group that is defined as being vulnerable and can only be studied by enrolling members of that group. Does that matter in the moral analysis?

DR. WENDLER: I think it is a wonderful question. A lot of people have the intuition that that makes a big difference. So, you see it in other cases of research with individuals who can't get informed consent.

So, for instance, if you talk about, what about doing research with people who have severe Alzheimer's disease, and you will get the response, "That might be okay, but only if it is to benefit other people who have Alzheimer's disease."

I think you have to think hard about what the basis of that intuition is. In most cases, I actually think it doesn't make a moral difference in the end. I think what is going on here is I think in a lot of cases that qualification, it has to benefit people of your

group or something like that.

Here is one problem with it: what is their group? You could divide children in so many different ways. There are European regulations that have this requirement and, then, they say, so it has to be people of the same age, the same religion, the same ethnicity, the same geographical area. You could just define. How about height? How about eye color?

Well, why do these things matter? I think they matter in competent adults because we think -- and I think sometimes this is true, but other times it is false -- we think competent adults care more or they are more interested in helping people who are conspecifics to them.

I think for a kid who is two years old, you just don't have any reason to believe that. But I think there is a separate consideration, which is what I mentioned before. It is this necessity requirement. You shouldn't be doing this on people who can't understand and consent, unless you have to.

If you look at the National Commission report, I actually think that is what they were trying to capture with this subject's condition requirement. One of the only objections that was ever made to the National Commission's recommendations was two Commissioners, one, Tuttle who was a lawyer in D.C. who really didn't like allowing kids with a condition to be in 406 but not healthy kids. He said, "Look, you are exposing kids who are already sick to more of this. That doesn't make sense."

Ken Ryan, who was the Chair, responded back, "You don't understand. In that case, we are doing research on that condition. So, we have to enroll children with that

condition."

I think Ken Ryan, and maybe some of the other Commissioners, were really confusing the subject's condition requirement with a necessity requirement. I think if we have non-competent individuals, the necessity requirement is really important. I think the subject's condition requirement doesn't make much sense.

DR. GUTMANN: Nelson?

DR. MICHAEL: Thanks for your testimony.

Do you think there is any moral or bioethical grounds on taking into consideration geography of where these kinds of countermeasures might be more likely to be employed in terms of where one might select volunteers for a pre-event research study?

DR. WENDLER: I heard that question this morning. I hadn't thought about that before.

I guess my initial response is, one, what you want to do in this research, you want to minimize the risk; you want to enhance the benefit. So, if you go to an area where you really have more reason to believe that there is going to be a problem, then that might be grounds for saying that there is more potential benefit for the people in that area. That would make sense to me.

Now my guess is that the ability to make those predictions is probably extremely low; I don't know. I am certainly not an expert in that.

The other thing that I think is interesting to think about, I mentioned subject selection. I think it is very important to have very clear, justified reasons for who you select to be in your studies. And I think that having these kinds of considerations, even

if your ability to predict isn't that great, I think the fact that you have objective considerations has a kind of value in itself, where you are not saying, "Look, we will just go and pick these kids because we can get them" or "because they don't understand" or "because their parents are more vulnerable." We have objective considerations that we are using. And I think there is a kind of public accountability value in doing that.

DR. GUTMANN: I have a question, too. One is you said that there are cases where we ask children to take risks for altruistic purposes, for strangers, we are talking about here. And so, I want to ask you, give me examples of where we ask children to take physical risks above the norm for strangers.

The two polls I have in mind are, on the one hand, we accept, I think a lot of people accept the idea of children taking extra risks for their siblings. The other poll, we reel against societies that have child soldiers, where children are being asked to take risks for their country that are physical risks.

So, I wonder what you have in mind in the area of acceptable physical risks, asking children to take more than what is common for strangers.

DR. WENDLER: So, first, let me say, you are saying "more than common". So, what would be common? My thought, and what I have been trying to do, is one way we do this is we just look and see what other activities, what other contexts where we allow children to face risks for the benefit of others, including unrelated others. There are lots of them.

I did a search a couple of years ago on a website on sort of volunteering for children that estimated probably in the U.S. each year more than a million children

volunteer for charitable activities to help other people that pose risks. So, these are all sorts of --

DR. GUTMANN: I am asking physical risks for unrelated. So, it doesn't count if you are a member of a track team --

DR. WENDLER: Yes, yes.

DR. GUTMANN: -- and you get the glory of your team winning when you push yourself the extra mile to exhaustion.

DR. WENDLER: Yes.

DR. GUTMANN: Physical risks for unrelated others. I just can't think of any.

DR. WENDLER: Oh, okay. So, here is one of my favorite examples. One of my favorite examples is car washes. So, there are lots of schools that have car washes where they take 10- to 17-year-old kids. Actually, I have this wonderful picture of a car wash where there are children standing by -- they are on the sidewalk, so they are relatively safe -- but they are standing by the highway and they have this big sign about "Car wash - come in here. We are trying to collect money for hurricane victims in Asia."

I think that kind of thing happens all the time. I think it is perfectly appropriate in most cases, if it is done right. But there are clear and very important, and in some cases serious, possible physical risks to those kids. The cars that pull in, they might get hit. They might fall down. They might step on one of the brushes that they are using and break their ankle. So, there are lots of actual physical risks.

One of the things I think we have to be careful here about where intuitions

work on risk, I think there is a way in which we sort of downplay those risks. Part of this has to do with the risk of daily life standard. I thought the National Commission was clever.

How do you figure out whether these risks are acceptable or not? If I just say to you 1-in-15,000 chance of death, is that acceptable or not? I think most people would say, "I have no idea. How do I answer that question?"

I think by basing it on the risk of daily life, it gives you a standard that allows you to try to make these sorts of judgments. I think that was clever.

I think the problem, though, is that a lot of risks of daily life for psychological reasons, we, in effect, just ignore them, right? If I say to people, "Look, when you put your kid in a car, you are posing risks to them," they will say, "No, I'm not. No, I'm not." So, you have to sort of get people to realize that there are those risks.

So, there are all these risks, all these sorts of activities. Having your child shovel somebody's sidewalk, having them mow their lawn, having them collect money for oxygen, having them do car washes. So, I think in those cases what we would say is we would say those are sort of what I would regard as giving us a standard for minimal risk.

Now you say more than that. I think those would be cases which would be very exceptional cases. So, I think you have to imagine a case. The extraordinary case you guys are thinking about is there's the threat or the actuality of a terrorist attack. I think that would be something like you have got somebody who is in serious trouble. You have got somebody who is drowning. You have got your 14-year-old child who is sitting next to you. You broke your leg. You can't get up. This is the only person who can save the person who is drowning. We just send them in. And I think, depending upon the

circumstances, depending upon the risks, depending upon your child, you might.

DR. GUTMANN: Let me ask a question from a member of our audience who is also a former presenter here, David DeGrazia.

"Your comments express an openness to considering indirect benefit to pediatric subjects. What about the potential for abuse of appeals to indirect benefits? Does that potential for abuse recommend sticking with the criterion of direct medical benefits?"

DR. WENDLER: Right. Good question. Yes, I think I mentioned this briefly in my slide. I do think that -- so, you might say this: you talk about these other benefits. A benefit is a benefit is a benefit. Why can't IRBs take those benefits into account in their deliberations? Why can't they think about, as the 407 panel suggested, helping a sibling? Why can't they think, as I am suggesting, the value of contributing to a valuable project?

I think the assumption of the question is right. I think that those are more worrisome in two ways. One is I think, particularly when you are talking about a 4-year-old, it is harder to decide whether or not and when those sorts of benefits really are benefits. How do you figure out for this 4-year-old whether helping their sibling is really beneficial psychologically to the 4-year-old? That is hard. So, I think they are harder.

I think there also is more chance for abuse. You could just exaggerate them because you can't measure them.

So, I would say, yes, more chance for abuse; we need to be careful about it. My response wouldn't be, though, to say we don't count them at all. My response would be to say that we should limit them to a kind of 407 panel where we get things like public

input. We have a lot of experts agreeing on it.

DR. GUTMANN: Christine?

DR. GRADY: David, thank you for your testimony.

Just following up on that, do you think that how valuable the project is needs to take into account any information about what kind of a threat there is? In other words, the uncertainty of any threat, does that take away from the value of the project?

DR. WENDLER: I think the chances that the project is going to be successful is really important in deciding what kinds of sort of what I call contribution benefits there are. So, to give the example I mentioned before, I think that there is a kind of important benefit to a child of pulling an infant out of a pond and saving their life. I think there is this way in which, obviously, it helps the infant, but I think there is this deep way in which it makes the life go better of the child who saved them.

That benefit is clearly greater than the chance of where you hear a scream and maybe somebody is in trouble, but who knows whether there really is? The first one justifies more than the second one, I think no doubt about it.

That is what I was thinking. It was interesting, people were talking this morning about, what about doing these once there is an attack? I have no idea about the logistics of that at all or the science of that. But I was initially thinking, well, why would that make a difference? But I can see at least one situation in which it might make a difference is just for this reason; it is because, then, the benefit is really obvious. I think there is a way in which you could say that now these kids are really heroes if they are doing something and they understand it.

Let me just briefly give you one of the analogies I have used before. If you look at civil rights marches, the march on Selma in the late 1960s, there was this big debate about using children in the marches. They ended up -- there was this huge debate between Martin Luther King and some of his followers -- he decided and they ended up using children in the marches. I am not a historian, but the historians tell me it was enormously effective to have children in those marches. They faced risks; there is no doubt about it.

DR. GUTMANN: You know John Lewis was one of those young people?

DR. WENDLER: Yes. And I think that they made an important, incredibly important, contribution to this country. I think what is interesting here is that these cases, there are actually very few situations in which children can make a contribution that adults can't make. It is very rare that that is true in life.

I think those marches were one case. The belief was that having kids there showing the problems with the policies that we had at the time, and the effect they have on children, was going to be uniquely powerful and valuable. It turned out to be right.

I think this is maybe another case. Adults just can't be the final ones to show whether or not a vaccine works in kids. You need kids to do it.

DR. GUTMANN: Just a quick one. You said subject selection is very important. Can you say some more about what you think subject selection should be to make it maximumly justified?

DR. WENDLER: I wish I had a really good answer for that question, but I don't. I think one thing I mentioned was, in some sense, I think it is sort of the negative value. It is making sure that whatever process you have, there are certain things you are not

doing, right? You are not picking on certain families. You are not picking on certain regions. You are not picking on certain children because they are just available, because they are easy, because maybe they don't understand as much. So, I think that is obviously really important.

The other thing that I think is important is -- this is just speculation -- but I think it would be really valuable if you could come up with some process by which -- I think you had mentioned something about a lottery, or somebody did this morning, which I don't think you probably could do that, but I think there is a value in that kind of an approach.

Here is my sense for a lot of these things: if you talk to people about giving to charity, if you talk to people about enrolling in research, a lot of people just don't do it. Why don't they do it? They don't think it is valuable? No. I think it is sort of like a collective action problem, right? They would be willing to do it if everybody else was willing to do it, but they don't know that other people are willing to do it.

So, I think if there were some way to address that concern -- I mean, a lot of these, I take it, not that you are going to be able to do, but some way of just saying, "Look, we are sort of all in this and we are going to have everybody have a possibility of doing this," I think that could be extraordinarily valuable.

DR. GUTMANN: John? And then, we have to wrap this session up.

DR. ARRAS: Okay. David, thanks so much. Terrific.

So, I am pondering how much justificatory freight this notion of being aware of contributing to a collective benefit can carry in your analysis. Okay? So, is this

meant to be a reason that can really be decisive or is it only decisive in conjunction with other considerations?

Because this will matter a lot once we go down from the category of young adults or teens who can, presumably, think about these things and derive pride and a benefit of the sort you described from participating, down to the lower reaches where we really need this information, too-- toddlers, infants, and so on. I mean, in that kind of a case, you can just have a kind of retrospective good feeling, like, "See, here is a picture of you doing this 10 years later," but at the time they have no conception of what is going on.

DR. WENDLER: So, the question here is, to what extent is there this, what I call, contribution benefit, contributing to a valuable product? To what extent is that valuable for the individual who makes the contribution? And what normative work does that do in the analysis?

So, I think, basically, the work that it does is that it can justify somewhat greater risks to which you expose the individual. Now how much greater risk I think depends upon a lot of things. Crucially, it depends upon the extent to which they understand and agree to be a part of it and the value of the study.

So, I think if you have got somebody -- David suggests you get a 16- or 17-year-old; they understand at least as well as the people in this room, probably would do better. I think if they really understand, they are really willing to take on those risks to help other people. I think that can justify a fair amount more risk. I mean, I think in that case that person is doing something that is truly heroic.

So, basically, I think you have three classes. There is that class. Maybe

that is people, kids typically 15 and older.

I think there is another class where we talk about assent, where they can understand some aspects of it, but they can't really understand the whole study. I think, for them, it can maybe justify like this minor increase, a little bit more but not a lot.

I think, the last class, children under that age who really don't understand at all, 2-year-olds, 3-year-olds, infants. This is, I think, more controversial. I think there are good arguments for it. I would be happy to talk to you about it. I think that doing that actually makes those -- it is in those kids' interest -- it actually makes those kids' lives go better, even if it happens at a time where they don't realize that they did it.

If that is true, I think it can justify a little bit more. But, given that they are not making that decision themselves, it is very little bit more.

DR. GUTMANN: Thank you very much. We really appreciate it, and you have helped us move our thinking forward. Thank you.

(Applause.)