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TRANSCRIPT

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DR. GUTMANN: Thank you. Could I invite our first presenters up to the table, please, and thank you all for being here. I thank you, before we get to ask you the hard questions, which you then may not thank us for being here.

We're going to begin our day with the discussion of Special Considerations for Research on Children because that's the fundamental issue that leads us to be dealing with this charge and we have with us Dr. David DeGrazia, who's a Professor of Philosophy at George Washington University. Welcome, David.

Dr. DeGrazia works on a wide range of issues and ethical theory, biomedical ethics, personal identity, philosophy of mind. He has authored or co-edited six books and published articles widely in journals, such as Philosophy and Public Affairs, the Hastings Center Report, Bioethics, Philosophical Forum, and the Southern Journal of Philosophy.

He's currently developing work on moral enhancement through biomedical means, the concept and science of suffering, and the definition of death.

Welcome, Dr. DeGrazia. We're very happy to have you with us today.

DR. DeGRAZIA: Thank you very much. Let's begin with what's at stake here.

Human research, of course, involves using human subjects and it often imposes risks on subjects, so human research requires moral justification. Much of the justification appeals to the prospect for significant benefit to society and here we're thinking about the future welfare of children. Meanwhile, paramount subject-centered values are subject self-determination and well-being.

We can understand these values of societal benefit and subject self-determination and well-being in terms of goals, rights, and protection from harm. The

goal of societal benefit is undeniably valuable but not all valuable goals can be pursued in just any old way. So we have to ask what means to this end are ethically permissible.

The crucial factor in setting limits, I think, to the pursuit of this goal are the rights of prospective subjects.

Human subjects, first of all, have a right to adequate protection from harm, although that, of course, will need to be specified. Competent adults also unambiguously have a right to self-determination. So in a qualified and limited way, I think, do most children and adults with compromised decision-making capacity.

But how should we understand these rights? At least in this context, I suggest that we understand the relevant rights as side constraints or trumps, as setting strict limits on the pursuit of even the most important goals.

Rights should not be taken as values to be balanced against the goals of research. One sometimes hears people talking about appropriateness of balancing the goals of research with subjects' rights. I think that's not the way to think about it because otherwise the vital interests of subjects might be swept away in the tide of appeals to societal benefit or social utility.

So how should we think about the rights of children in research? We should, first off, bear in mind a couple of factors. Their vulnerability to domination and exploitation by adults, parents, guardians, authority figures, including researchers, and their limited decision-making capacity.

Let's now consider a couple of decision-making standards that are lexically ordered in the sense that if the first one applies, the second one doesn't come into play.

First, informed consent for those subjects who are competent adults or

subjects determined to have sufficient decision-making capacity and then, second, best interests for children or for adults who lack sufficient decision-making capacity.

But the interpretation of these standards is complicated by a couple of factors, the fact that children have partial decision-making capacity and ambiguity about what constitutes best interests.

The informed consent standard rests on the assumption that the subject has decision-making capacity, but what is that? I think of it as the capacity to make a decision of the relevant kind autonomously. The decision could be financial, it could be interpersonal. Here, it's about whether or not to join a protocol.

If decision-making involves autonomous action, we face the controversy over what constitutes autonomous action. It's a very complex issue in literature. I've weighed in on it but I will not here propose the analysis I suggest for philosophical purposes, thank goodness; rather, I will suggest what I think is a little bit more practical for this context and which bears the significant influence of work by Beauchamp and Childress and Faden and Beauchamp.

These are conditions for the informed consent which I understand as the sufficiently autonomous authorization for participating in research.

One provides valid, that is, voluntary informed consent, if and only if one consents to participate in a protocol intentionally, with sufficient understanding of the nature of the study, its risks and possible benefits, and sufficiently freely of both external constraints and internal constraints.

Some mature minors are probably capable of informed consent, even though they count as minors under the law. All other minors are not. They tend to lack sufficient understanding and/or sufficient freedom from such external constraints as

their dependence on adult authority and the internal constraints that are associated with their own immaturity.

But autonomy and capacity come in degrees. They're not all or nothing. That means most minors have them to some degree and we should therefore take the minors' wishes into account as to whether he or she wants to participate in research.

Accordingly, I think the common practice of requiring the minor subjects' assent, along with proxy permission, is a good practice. I note, however, that some exceptions are possible and, if appropriate, we can talk about those later.

Meanwhile, the best interest standard applies to nearly all minors. It's generally understood to permit research on children when there's only minimal risk or a minor increase over minimal risk, if certain conditions are met, or direct medical benefit that compensates for any risk.

But note. If we take the language of best interests in a literal maximizing way, this standard presumably prohibits research on children whenever they face any risks that are not offset by the prospect of benefit to them because the concept of best implies a kind of maximization.

I suggest that we not take this term so literally. Instead, I think we should understand the best interest standard as protecting minor subjects' essential interests. This extends the idea that parents owe their children protection of their essential interests, including adequate protection from harm, but what constitutes such protection from harm in the context of pediatric research?

Well, here I recommend a general standard, one that surely would need to be specified for specific contexts, but I think it's ethically sound.

Children may be involved in promising research that either offers direct

medical benefit that compensates adequately for any risk or no direct medical benefit but relatively minor risks that are compatible with the protections that responsible parents would afford their children.

So here, there's an appeal to what good responsible parents would do in protecting their children and making decisions for them. It leaves a lot open to discussion but it's somewhat analogous to the way in which the law sometimes appeals to the reasonable person.

So if this standard is right, then pediatric research, outside of these categories, violates children's right to adequate protection from harm and since we should understand rights as limits or side constraints, that would mean that research falling out of these categories just should not be done.

Thank you.

DR. GUTMANN: Thank you very much.

DR. DeGRAZIA: You're welcome.

DR. GUTMANN: We're going to save our questions until after both speakers present.

Our next speaker now is Dr. Robert "Skip" Nelson, who is currently the Senior Pediatric Ethicist in the FDA's Office of Pediatric Therapeutics.

Among his other duties, he is Co-Chair of Pediatrics and Maternal Public Health and Security Action Team of the FDA Medical Countermeasures Initiative. Immediately prior to joining the FDA, Dr. Nelson was Professor of Anesthesiology, Critical Care Pediatrics, at the Children's Hospital of Pennsylvania, Philadelphia, and on the faculty of the University of Pennsylvania School of Medicine.

Dr. Nelson served as a Member and former Chair of the FDA Pediatric

Advisory Committee and the Pediatric Ethics Subcommittee as well as a Member of the Subcommittee on Research Involving Children and the Secretary's Advisory Committee on Human Research Protections.

He was also a Member of the Committee on Clinical Research Involving Children at the Institute of Medicine and a Member and former Chair of the Committee on Bioethics of the American Academy of Pediatrics.

Dr. Nelson, the floor is yours.

DR. NELSON: Thank you, and thank you for the opportunity to address you this morning.

I don't think you'll see too much areas for disagreement between David and I as I work through my slides, but in our discussion perhaps we can extend the envelope a little bit.

I think at this point, we understand that we should protect children through research as opposed to protect children from research and because of that, we have an obligation to assure that there's adequate data for the safe and effective use of drugs, biologics, and devices, in infants, children, and adolescents.

This need for data underscores our responsibility to make sure children are only enrolled in research that's both scientifically necessary and ethically sound and children, of course, are considered vulnerable persons and thus require additional protections.

I'm not going to go through the outline. You'll see this multiple times through the presentation, but I'll start with the basic ethical framework.

There are four principles that I like to cite as a basic ethical framework. The fourth principle of parental permission and child assent I won't be dealing with.

The first one is that children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally.

Second would be absent a prospect of direct therapeutic benefit, the risk to which children would be exposed must be low. In other words, knowledge does not justify more than low risk.

And children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary healthcare.

I'm going to walk through how these ethical principles are then developed within our regulations.

The first principle of scientific necessity I link to the requirement for equitable selection. If you look back at the National Commission's report, this is where they spoke about the obligation to enroll adults before children and not to enroll children unless essential.

There's two practical applications of that principal if you look at FDA decision-making. One is the use of extrapolation which I'll talk about in a subsequent slide. The other is the use of the FDA Animal Efficacy Rule which I hope you will become familiar with since this is an important rule in developing medical countermeasures.

Recently, Levofloxacin was approved for the treatment of pneumonic plague on April 27th, based on animal work that was presented both by a sponsor and work on Ciprofloxacin that was done by NIH.

Now the other two principles I like to frame within what I call the low-risk

pathway and the high-risk pathway. We need sufficient data, either from animal models or adult human clinical trials, to conclude either that the administration of the investigational product presents an acceptably low risk if there's no direct clinical benefit to that child and the language in our regulations are minimal risk and minor increase, or if that product presents a higher risk that there must be a sufficient prospect of direct benefit to justify those risks, where the balance of that risk and potential benefit is at least as favorable as available alternatives, and that frames the three categories that we find in Subpart D in our regulations.

So I'm going to walk through some key concepts as part of these regulations. First is prospect of direct benefit. First of all, it's a benefit for the enrolled child. It's based on the structure of the intervention and not intentionality. The level of evidence that you need is lower than that of efficacy, otherwise it's an infinite loop, can never get there, whether it's sufficient to justify the risks is a complex judgment, similar to clinical practice, and basically the child should have as good a chance for benefit as the clinical alternatives.

Now extrapolation basically is where the course of the disease and the effects of the drug are sufficiently similar that we can conclude from adult efficacy trials that we can get safety in dosing studies in pediatrics and say that it would work in pediatrics.

There's different approaches to that. We may not require any efficacy studies or we may require partial studies that can confirm our ability to extrapolate. There is a published article on this in Pediatrics that I can give you the reference to, it's not on this slide, if you'd like more information about it.

But extrapolation is an important concept as we look at pediatrics. Here's

one example where both prospect of direct benefit and extrapolation worked together. One is in the proposal to enroll adolescents in an HIV vaccine trial.

The first point is that you would not enroll adolescents until the adults showed a sufficient prospect of direct benefit to justify that enrollment, based on cell-mediated immunity.

The second would be if we could extrapolate, we would not need a large enough sample size to where we would do adolescent efficacy but could still end up with concurrent licensing because we've enrolled enough adolescents to make a descriptive comparison between their immune response and the adult immune response, and there's a publication where you can read more about this.

Component analysis is another important idea. Protocols can contain both procedures that do not offer prospect of direct benefit or procedures that do offer prospect of direct benefit and basically you need to take that protocol and analyze it in those component parts.

If you don't do this, the concern is that you could end up with an intervention in that protocol that does not offer a prospect of direct benefit but that exceeds the acceptable limits of a minor increase over minimal risk, unless you referred it for federal panel review.

Here's one example of a trial that used placebo administration that went in for IV infusion four hours each day for 14 days. A limited number of sites in this trial actually approved the use of a central line without adequately considering that this meant that you were placing percutaneous central lines into children that were in fact going to receive placebo and this was felt to be inappropriate and that they should have sought other ways to maintain blinding than putting in central lines in kids that needed

placebos.

Finally, the low-risk pathway has this notion of disorder or condition which is important to consider. Generally, I didn't offer you the definition of minimal risk but we don't consider administration of an investigational FDA product to be minimal risk. It's not what we normally do in the course of every-day life in children, etcetera.

The minor increase over minimal risk category has this language about disorder or condition and the need to generate generalizable knowledge that's of vital importance for understanding this disorder or condition.

There's no definition within our regulations. Here is one definition that was proposed by the Institute of Medicine in their 2004 report, where you look either the disorder or condition as the child has a disease or it is at risk for a disease, and so this notion of being at risk for a disorder or condition is an important aspect of deciding whether research is appropriate or not, and here's one example of that.

Single-dose pharmacokinetic studies of over-the-counter cough and cold products, you may know, if you were looking at the press a couple of years ago, we don't have a lot of information about how to appropriately dose children with over-the-counter cough and cold products. So to get this, you need to do pharmacokinetic studies.

The question is can you do that in any child or do you need to do it in a child that has a disorder or condition and here's a definition of asymptomatic children who may be at risk, based on their frequency, crowding, and exposure to potential individuals with colds that would help define an at-risk population as opposed to just doing pharmacokinetic studies in any child.

Finally, some comments on the escape hatch. So what I've walked through with you is these three categories of research that's the sort of basic paradigm: minimal risk, minor increase over minimal risk, and then prospect of direct benefit.

The National Commission specifically used the term "escape hatch," which is why it's here in quotes, where they felt that it was possible that there may be other research that they had not adequately characterized in these other three categories that may still be important but that should proceed with three key aspects of the discussion.

First, that there should be a public review and comment and so it shouldn't be an administrative procedure but something that has oversight by society.

Second is that it should be in accord with sound ethical principles and that such a protocol should apply but not suspend the ethical principles of respect for persons, beneficence, and justice to this new and unanticipated state of affairs.

What's interesting is in their initial draft of this, they specifically refer to the principles of the Belmont Report, which is what's contained here, but then in the subsequent drafts changed that to sound ethical principles, raising the question as to whether there's another principle that they had not characterized but, unfortunately, I don't think they did characterize that and therefore you have your work cut out for you.

And then, finally, a serious health problem, not necessarily limited to a national emergency but of major significance.

Now I should say they thought there was going to be a national advisory board but this was not established until 2003 when the FDA Pediatric Advisory Committee was chartered to do these kind of reviews.

Here are the required findings for these public panels. Either the panel

could find that it's approvable but under one of the other three categories or that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem. Again, it would be conducted in accord with sound ethical principles and adequate provisions for assent and permission.

I've walked you quickly through topics of the basic ethical framework, some key concepts, and then suggested some ideas around this federal panel review and hopefully will have adequate time during our discussion to flesh out some of these concepts.

DR. GUTMANN: Terrific. You both did great in staying within your time, which means that you'll have more time to answer questions that are directly relevant to our charge, and I want to open it up to any members of the Commission to begin and John, let's start with John Arras.

DR. ARRAS: Yes. Thanks to both of you. What I find puzzling about this is that, of course, there's no real content given to the notion of sound ethical principles here. Okay? So, in other words, they're just punting it upstairs to folks like us.

So what I'm wondering is, is there a track record here at FDA or wherever where cases of this sort have been adjudicated?

DR. GUTMANN: Skip, do you want to begin?

DR. NELSON: Yes and no. So there have been referrals under either 45 CFR 46.407, which is the ATHS one, or 5054, which is FDA.

Prior to 2003, there were some informal referrals and then after 2003, there have been, I think, five, but the bulk of those referrals, in fact all of them, I think, since 2003 fit into what I would call the desire to have a normal healthy control group,

to make a comparison to a group of children with a disorder or a condition in a research study that presents only a minor increase over minimal risk, and so what that has done -- and there's individuals who have argued in the literature that this distinction between children with a disease and those without a disease around minor increase over minimal risk is problematic and that you can come up with an understanding of responsible parental decision-making that would cover parents making decisions to enroll healthy children in research that truly fits a minor increase over minimal risk, and so those protocols, by and large, have been allowed to go forward under 5054.

Enrolling children without a disorder or a condition in research, it was considered a minor increase over minimal risk.

There's no example I can think of that has been approved where it goes beyond a minor increase over minimal risk. A couple of analogies. There was, prior to this formal process, there was a dry vax vaccine example which you could get into in conversation that didn't go through a panel process. It was an open process because one didn't exist at the time.

We did have an advisory committee meeting where we explored the question of whether it would be appropriate to do a non-therapeutic brain biopsy for the purpose of genomic, pharmacogenomic testing in children who didn't need the brain biopsy. That was not an official panel referral but I will say the results of that were ambiguous, at best. The vote of the panel was in favor of doing that but it was basically the scientists split pretty much evenly and most of the ethicists, except for one, were against it. So the vote came out barely in favor of it but was highly uninformative in my view about whether such a protocol should have gone forward from an ethical perspective.

DR. GUTMANN: Skip, let me just ask you a factual question which will help clarify what the baseline here is when we get to children and developing countermeasures.

Is there a vaccine, anthrax vaccine against adults, and does that allow us to extrapolate that there could be a safe one developed that could be tested at minimal risk for children?

In other words, that's a big question but I think we need some baseline here as to what the factual records suggests about one of the time questions we're very specifically being asked to answer.

DR. NELSON: The anthrax vaccine is approved for adults for prevention. I mean, it's disbursed in the military and given under that indication. It is not approved for what would be called post-exposure prophylaxis. In other words, in the case of an event, you would then deliver it.

So for adults, based on the known information about using it in the pre-event setting, it could be administered under what's called an emergency use authorization if there was an event.

There's no data in pediatrics at all and --

DR. GUTMANN: There's no data in pediatrics at all --

DR. NELSON: Correct.

DR. GUTMANN: -- on this?

DR. NELSON: Correct. So the mechanism if there was an event for disbursal of that agent from the stockpile would be under IND and so that it would still be considered an investigational drug, and there's some implications of that. It wouldn't be under an emergency use authorization.

So one of the questions is could one generate data prior to an event that could allow you to do it under an EUA or not, but there's no data. So you would have to, at the very least, if you would allow for extrapolation of efficacy, you would need immunogenicity data to know that X dose gave you a protective response that would mimic that of adults which is what's done with influenza, for example.

Each year, there's immunogenicity testing that just helps you establish that this dose of the virus will get you this level of protection.

DR. GUTMANN: Could you say something on influenza, just so we know, on how it is extrapolated for children?

DR. NELSON: Well, yes, I will, but I'm not a representative of the Center for Biologics, so take this as an ethicist providing you my knowledge about the FDA which I think is pretty good but still might have some holes.

But basically, if you look at something -- I mean, H1N1, H1 -- I mean, there's a lot of information about what level of immunogenicity you need to provide protection against influenza and so as you look at the --

DR. WAGNER: Adult information or also --

DR. NELSON: Pediatrics, as well.

DR. WAGNER: -- pediatrics?

DR. NELSON: Absolutely. There's a lot of -- so when you look at issues of strain change, so you have your basic package of the virus and you want to say instead of this strain, we put in that strain, all you really need is immunogenicity data in a hundred people, small numbers of samples to just say we know this is the right dose that's going to get you protected.

So the amount of data you would need on a vaccine may not be extensive

as far as immunogenicity data to be able to say that you expect that you would be protected. So at the very least, say in anthrax, one would need pediatric immunogenicity data to know that you get the same immune response that you would get in adults which has been established within the military experience.

DR. GUTMANN: I have everybody here. So let's start with Nelson and then go to Jim and go to Christine and we'll move on.

DR. MICHAEL: I just have a very quick follow-up.

DR. GUTMANN: I do want Alex to say something, as well, and please, if you have any questions there, staff, just move them up. Yes?

DR. MICHAEL: Just a very quick question or clarification to Dr. Nelson, which would be in the situation you just described, you have to have a correlative of risk of infection or a correlative of mechanistic protection. That comment actually bears weight.

I think there's some ambiguities. Certainly in my field in HIV, there is, even with our recent elucidation of some correlates of risk in one vaccine in one study, we're not sure that's going to convey to other populations or other vaccines.

I just think there's definitely going to be imprecision scientifically on that kind of bridging study.

DR. NELSON: Yes, I think that's absolutely essential. Extrapolation is based on having some ability to bridge and we can bridge in influenza. We may be able to bridge in anthrax. We cannot bridge currently in HIV.

DR. WAGNER: Skip, in developing the pediatric data that we're talking about, when we looked at your initial -- early in your slide sets, your initial four conditions, Number 2 is the one that talks about, especially maybe particularly in the

case where there's no prospect for direct benefit, that there be low risk.

Is low risk in your mind defined differently for a pediatric population than for adult human subjects?

DR. NELSON: The definition of minimal risk is no different within our regulations. It's defined as every-day life or routine physical and psychological examinations.

Ethically, however, every prior federal panel, as well as the IOM report, said that minimal risk ought to be interpreted against the life of a healthy child. In other words, we shouldn't expose children with a disorder.

So from that standpoint, one could say ethically that how you interpret that within Subpart D might be different. I won't comment on whether the adult ethicists should think that. I think in pediatrics, we do that.

So from that standpoint, I guess the answer would be yes.

DR. GRADY: Thank you both for very nice comments.

I want to focus on the specific question of countermeasure research because it seems as if, by definition, it's not direct benefit. It's not prospective direct benefit. It's not minimal risk. Almost anything that you can imagine would be countermeasure research, and there's no subject condition, unless you want to argue there is at-risk and I'd love to hear if you do.

So we're already in the territory of something really important and sound ethical principles, right? So I guess my question to both of you is, I mean, one way to interpret what you said, David, is that it shouldn't be allowed. I want to see if that's what you mean.

Skip, maybe you were suggesting there's another ethical principle that

might help us. Do you have in mind what that is?

DR. GUTMANN: So, David, why don't you begin? Is the implication of what you have said that they should not be allowed? There's no direct benefit?

DR. DeGRAZIA: I think it's not all that clear for a few reasons.

One is that direct benefits can be either immediate or future and if testing conferred some immunity on an individual, it's conceivable that in the future they would benefit from that protection from anthrax. So that's a factual matter that would have to be explored.

Another is I recently spoke to someone who's an expert in pediatric research who thought maybe the risks would be within minimal but let's assume that that's not correct and that you're right, that they would not be minimal.

DR. GUTMANN: So could I just clarify before you go on?

DR. DeGRAZIA: Yes.

DR. GUTMANN: So you would say if the risks are minimal, even if the benefit is not direct, then --

DR. DeGRAZIA: Yes.

DR. GUTMANN: -- it could be justified?

DR. DeGRAZIA: I think so because --

DR. GUTMANN: I think that's important just to clarify.

DR. DeGRAZIA: Yes, yes. And the reason is that I think that that standard so often appealed to of minimal risk is within the standard that -- the scope of the standard that I suggested of what good responsible parents would have for their children.

DR. GUTMANN: Right. I just wanted to establish that. So you two are

agreeing on that?

DR. DeGRAZIA: I think so. One place where we may disagree is that Skip talked of the possibility that maybe there are some other principles out there that might justify some exceptions.

I think not. I think if there's anything that would justify exceptions, it's already there front and center called beneficence, a particular societal benefit, and I also argue that we understand rights more or less as trumps or side constraints which implies strict limits on the pursuit of even the best goals.

However, strict does not necessarily mean absolute and I think of human rights as not quite absolute and so even, I think, in the best of ethical theory, best of rights theory, it is acknowledged, as sometimes in great emergencies, rights can be overridden in the least overriding way in the name of societal benefits. So even in my analysis, it would not absolutely rule out research that would fall outside of the categories.

I realize now that I actually did pretty much say that but I was -- the emphasis on the strict limits is basically the idea that instead of thinking of goals and rights as things to be balanced, we think of rights as setting the limits to the pursuit of goals with very few exceptions.

DR. GUTMANN: So just to clarify what you've said and this relates to what Skip said, the Belmont Report had a principle of beneficence in it and what David is saying is you don't have to go beyond that principle to get something, the framework that one would need.

The second thing you said is that there's always an emergency clause to rights but emergency clauses don't deal with small probabilities that something might

happen. Emergency clauses mean we have an emergency here and in an emergency, when the world is at risk, we are open to thinking of the least possible violations of rights to save the world or to save one society.

So the emergency clause isn't going to work for our thinking about testing children now for a possible emergency later. That's not what emergency clauses in moral arguments have ever been used for. They've been used for --

DR. DeGRAZIA: That's true, yes.

DR. GUTMANN: -- there's a clear and present danger and so I just wanted to make that clear.

DR. DeGRAZIA: Yes, that's true.

DR. GUTMANN: It might work in the case of an emergency but we're not right now facing an emergency.

DR. DeGRAZIA: Right. There's always an issue of how you define emergency but I think what you say is well taken.

DR. GUTMANN: Okay.

DR. DeGRAZIA: And also, by the way, the concept of emergency is somewhat metaphorical. It doesn't have to be taken literally. It means situations in which societal utility are so much at stake that they might justify such actions.

DR. GUTMANN: There are clear things in --

DR. DeGRAZIA: There are real emergencies.

DR. GUTMANN: Where there's a fire and --

DR. DeGRAZIA: Those are literal, right.

DR. GUTMANN: -- nobody knows it but I see there's a fire and we clear everybody out, no consent. We've cleared everyone out because everyone's going to die

if we don't. So the concent goes by the board there.

DR. GARZA: Marshal Law.

DR. GUTMANN: Barbara? What?

DR. GARZA: Marshal Law.

DR. GUTMANN: Marshal Law, which could be overused, but you have to be careful, so you have to be -- but there are times when you have to use it.

Christine, you want to follow up?

DR. GRADY: I just wondered if Skip can answer.

DR. GUTMANN: Oh, yes. Skip. I'm sorry.

DR. NELSON: Just a couple of quick comments. So all medical countermeasures are not created equal and so you have ones where we repurpose. Ciprofloxacin, Levofloxacin would be an example. Pyridoxine for which we have data based on organophosphate pesticide poisoning happens to be labeled for use for Sarin gas if you had that kind of an example.

Then you have anthrax and smallpox at one extreme and you've got influenza and different kinds of ranges where how we assess risk is very different.

The other problem is individual risk assessment. I don't think -- I mean, I would not be arguing if we went to testing in a pre-event setting for anthrax vaccine, that we would obviate parental permission and child assent.

So the question is to what extent we as a society think it's appropriate to put that decision in front of a parent, and I could imagine parents, depending on their experience and their own assessment of risk, feeling very differently about that, depending on whether you're in the military or whether you live in Washington, D.C., and go to public schools or whether you're in New York City and so forth.

So now I think you have a panel that's going to be trying to tackle this question of whether there's other ethical principles. I know some of the ones that have been suggested might be public health principles, solidarity, and so forth, but those in many ways could only be seen as reasons why a parent might choose to do something that other parents might not choose because I don't think any of us -- I'm certainly not arguing that we should proceed with testing absent voluntary parental permission and child assent wherever that's feasible.

DR. GUTMANN: Yes. You should, for the sake of the record, put Number 4, unless you just skipped over it, it wasn't actually there.

DR. NELSON: It's a footnote to the Slide 3. It says Number 4, Parental Permission.

DR. GUTMANN: Okay.

DR. NELSON: It's a footnote to that one that's there but that's an important point.

DR. GUTMANN: It's worth elevating it from a footnote because it's an important point.

DR. NELSON: In 10 minutes, it got chopped.

DR. GUTMANN: No, no, no. That's fine. Your presentation was fine. Just for the record.

Barbara?

DR. ATKINSON: My question was very much like Christine's but just as a point of fact, and I assume it's true, for adults in the anthrax specifically, is it true that it would be considered only a minor increase in minimal risk?

I mean, does that vaccine itself fall into that category for adults?

DR. NELSON: Two comments. We don't use that risk categorization for adults. I mean, with consent, they can expose themselves to much risk for whatever --

DR. ATKINSON: Right. But if you were going to?

DR. NELSON: Personally, I think not, but risk assessment --

DR. ATKINSON: You think it's higher?

DR. NELSON: I think it is higher than a minor increase over minimal risk, but we could get a bunch of pediatric ethicists around this table and have a very robust discussion about what's minimal risk and what's a minor increase over minimal risk.

DR. GUTMANN: Alex?

DR. GARZA: Sure. First of all, those are terrific presentations and I thank you both for that.

So one of the big -- so I was at the exercise that really spawned all of this discussion about pediatrics and medical countermeasures and so when the exercise is going on and you're feeling the weight of your decision-making, then you walk it back to how can we prevent something like this from happening and so the exercise, of course, was a bioterrorist attack and how do we prevent loss of life, and one of those decisions, of course, was immunizing people post-event and then how do we protect children post-event, and there was no answer, which for us as decision-makers in the U.S. Government, is not a good answer when you have no answer.

Which then led us to the discussion that we're having today and so what I frequently entail in my job is the view of risk and so traditionally what we run up against is I think there's a very understood definition of risk which is based off of historical data.

You had mentioned the flu. We can always see what happened in previous flu seasons, how previous vaccines have reacted against previous flu viruses, and we have a pretty robust amount of information that can describe what the risk profile is.

We're not so lucky when it comes to very extreme issues, such as anthrax, bioterrorism, chemical weapons, especially with biological weapons, just because there's no real structure for us to look back and say, yes, this is minimal risk or this is high risk.

And so I guess my question is, is there a qualitative shift in the risk-benefit paradigm that both of you are advocating for medical countermeasures for children when you are dealing with a risk profile where you don't have a lot of historical data to say this is absolutely the risk to this population instead of these are the possibilities that could happen in the course of an event.

DR. DeGRAZIA: I think the answer is no for me. I don't have -- what was the phrase you used? Quantifiable?

DR. GARZA: So when you're looking at risk, frequently our risk paradigm in a security or in defense apparatus is much different than a risk profile, I think, with other normal medical issues because we deal with events that are low probability but very high consequence and so should we consider different risk profiles, such as that, and I understand there still needs to be an individual protection, as well, but is there a different way of thinking about risk when you're thinking about issues, such as the low-prevalence but high-consequence profile, instead of something that is very common, such as influenza?

DR. DeGRAZIA: Well, the sort of disaster that you want to prevent is

very great and so if and when any exceptions to rights claims are justified in the name of societal utility,that would -- the sorts of consequences that you're talking about could be factored in.

We use the concept of emergency to talk about sort of an escape clause from the usual protection of rights and I mentioned in my exchange with Dr. Gutmann that emergency can be construed literally or it can be construed somewhat metaphorically to refer to situations in which the apparent gains in utility are so great that overriding rights might be justified, and I note that this is a difficult area of ethical reasoning.

I continue to resist the image of rights as something just to be balanced against goals, but I also resist the idea of, at least in the case of most rights, absolute rights.

So the picture is somewhat unclear to me about when you have enough gravity in terms of the utility at stake to consider such a thing. If it were to be considered, it might make sense to begin with minors who are as close to mature minors as possible because then they're closer to being able not only to assent but give consent and then it might be possible to do some extrapolation downward and minimize the overriding of any rights, if in fact that's the right thing to do.

So I'm not answering your question with great certainty because I'm not sure where to draw the lines but I think now I have a better understanding of what your question is than I did at first.

DR. GUTMANN: So let me just offer a framework and see if this makes sense. We'd still have to plug in facts into it, some facts. I mean, some facts are in this framework.

So we in an earlier report talked about the principle of responsible stewardship, which is a more specified version of public beneficence. It's that we should be responsible, take responsible action to make sure we don't impose bad things on people who can't protect themselves individually.

So responsible stewardship is a principle that may come into play in this case. So what Alex is saying is imagine an uncertain probability but let's say it's a small probability but extremely high-impact, large catastrophe, if it happens.

If there's a minimal risk in what we're doing now, in what we'd have to do to protect against it, so that's where we don't have the fact right now, but assume a minimal risk, one would go forward with trying to do something with the appropriate consent form in place, is that right, by both of your frameworks?

DR. DeGRAZIA: Yes. You said it's still within minimal risk?

DR. GUTMANN: It's still within minimal risk, if it's still within minimal risk. So the real problem comes if we don't know that it's in minimal risk and we don't know right now whether it is.

DR. DeGRAZIA: Well, I think --

DR. GUTMANN: If it's in minimal risk, let's just --

DR. DeGRAZIA: Yes.

DR. GUTMANN: Then there's a way of moving forward, correct?

DR. DeGRAZIA: Yes, yes.

DR. GUTMANN: Okay.

DR. DeGRAZIA: Right. Well, the standard I suggested didn't really refer to minimal risk but I suggested it was compatible with it which was what good responsible parents would allow for their children. I'm not sure that comes to only

minimal risk. It's something that --

DR. WAGNER: Low risk.

DR. DeGRAZIA: Some kind of low risk.

DR. NELSON: That's why I used the language of low risk was to take minimal risk and minor increase and sort of lump it together and this notion of responsible parent is one that I would support, as well, in trying to understand that low-risk category.

DR. GUTMANN: I'm not sure I understand the difference between minimal and low risk but I know there are other people who want to --

DR. WAGNER: I just want to say as we continue to massage your framework, which I like very much, I want to make sure that we talk about one other variable category of risk.

Your talks focused most, it seemed to me, on the category of risk associated with exploring therapies and vaccines, and Alex and Amy just introduced, well, how should we think about the risk you've been describing when we also take into account the category of risk that I would associate with biological threat? Maybe it is low probability, high risk, and you've just allowed if it's minimal, it modifies it.

If your risk is much lower than the other, it modifies it considerably. Presumably that's the reason we continue to give polio vaccines in this country, in spite of the fact that the incidence rate -- well, it's zero and the risk may even be lower than anthrax attack.

The third category I just would like to -- I'm sorry. That was an opinion. Don't use that.

So the first category is around understanding therapies and prophylaxis

and vaccine and we're wondering if we can modify that, if it should be modified by the kind of risk of biothreat.

Is there a third category that should factor into her calculus, in Amy's calculus, around the risk of untested deployment in the case of an actual threat eventuating? Sorry for the long question.

DR. DeGRAZIA: Right. Maybeso. I raised the question in passing before whether it might be fair to talk about direct medical benefit to some recipients of the tests that are being contemplated because if they're effective, they may help an individual later if there is an attack. That would not be an immediate benefit. It would be a future one and also be speculative and so to those extents, they should count less than an immediate direct benefit.

But you're raising the question of what baseline, I think, of what baseline we should compare the situation of those who are prospectively enrolled, prospective subjects for trials and whether the fact that they may --

DR. WAGNER: No, no, no. I was talking about actually deploying in use. What is the risk, for example, of under-dosing large populations because you hadn't done the testing to determine the immune response and you actually have a more catastrophic result?

DR. DeGRAZIA: Okay. You're talking about risk to the society?

DR. WAGNER: Yes.

DR. DeGRAZIA: Not to individuals?

DR. NELSON: Just a couple of quick comments. I think it's very important to parse risk out and to recognize when we're using the term, we're referring to very different things. The risk of the intervention, the risk of the disease that may

occur based on the nature of the threat, etcetera.

A couple of quick comments specific to anthrax, let's say, compared to smallpox. I mean, anthrax is treatable by Ciprofloxacin, Doxycycline. In other words, there's no urgent need to vaccinate, provided people take their antibiotics, you know.

So as opposed to smallpox where, if you want to prevent an outbreak, you have to basically come in the same way we eradicated it and vaccinate immediately around that, etcetera, because there's no specific treatment for that.

So the reality is that vaccination is you don't have to get people vaccinated day one but they have to be vaccinated before they stop their antibiotics which is often around day 45, but then the debate is how many people are going to take 45 days of antibiotics? Likely low. We probably don't do that as consenting adults. Can parents get that into their kids? We could begin to debate that.

So I think those are very important facts that need to be kept in mind as we think about these different scenarios.

DR. GUTMANN: Good. Dan? Very patient.

DR. SULMASY: Thanks. Yeah. I think we have to acknowledge that the prospect of direct benefit to the children is exceedingly low. Even in the vaccine, in general, is exceedingly --

DR. GUTMANN: Yes, yes. Absolutely.

DR. SULMASY: -- low and that the benefit we're talking about is social, right? It's the real way we're talking about it because of the high impact of this, maybe even because of herd immunity to prevent if there's a breakout that people don't take their antibiotics, that we get enough people treated, that we're not spreading the disease to others.

But in the end, I think you said, Skip, that maybe we need another principle, like solidarity. I would like to go there but I suspect that Americans typically don't like to invoke that because I think, particularly here, it pushes against this question of whether we're exploiting a vulnerable group for the social benefit that we see and that's the real worry.

So what it seems to me may be a way out of this, and I want both of you to consider this, is in a case like this, the benefit, the social benefit would redound to the class that makes one vulnerable in the first place and can only be obtained by having volunteers within that class. In this case, those are the children, right, and does that make a difference then, provided we then have low risk and provided we have parental consent? Does that part of it give us a little more room in a case like this?

DR. GUTMANN: And that's going to be the last question, so good answers for this one, as you have for the others.

DR. DeGRAZIA: So is the question does it make any difference that at least the class of the subjects, children are the ones who would benefiting later?

DR. SULMASY: And if it can only be obtained by having -- if you want to get dose response in children, you only get it by children volunteers.

DR. DeGRAZIA: I know a lot of people think that that's morally relevant. I have to confess that I don't because all of us, we're all members of many different groupings of people and classes, and I don't think that is a morally relevant consideration, but I realize a lot of people disagree with me on that.

DR. GUTMANN: Skip?

DR. NELSON: And this might be one point where I would, actually. I mean, I think if you look back at the principle scientific necessity, it's based on that

argument that, in fact, you should only enroll children in research that would in fact be for the purpose of getting information that's relevant to the public health of children and not for some other class, although I agree we can get into a fine analysis of class that would be problematic.

I guess my only final comment is all of this needs to be informed by good facts. Herd immunity is not relevant to anthrax. I mean, they dust Washington. It's because we can't decontaminate the place well enough to then re-inhabit the city, so we would need to be vaccinated for that purpose, whereas herd immunity for smallpox would be.

And the other would be if we want to look, for example, at immune bridging and want to do testing of different doses and that sort of thing, we would need first that data in adults to know that we would have a knowledge of what dose pairing would happen with adults and so the ability then to do certain pediatric trials also depends on seeing how that relationship is with the adult trials and the ability then to do that bridging would depend upon what we're bridging to.

So each medical countermeasure, as you get into the weeds, can have slightly different variations around how one would approach the issues that that testing would take.

DR. GUTMANN: So this is the perfect segue because our next session is on Practical Challenges Posed by Pediatric Research, but before we do that, get to the next session, we owe you a great thanks for two terrific presentations and great responses, too.

(Applause.)

DR. GUTMANN: Thank you.