Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

Member Discussion

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DR. GUTMANN: Good morning. I am Amy Gutmann and I am President of the University of Pennsylvania and Chair of the Presidential Commission for the Study of Bioethical Issues and I am particularly thankful to my vice-chair, our fabulous leader, Jim Wagner, for taking over the helm yesterday. I was told that this chair was with my name and empty and I said I hope it wasn't like the appearance of President Obama at the first debate only worse because he showed up and I didn't, but I read the transcripts of yesterday's--it wasn't an official transcript, but I read the summary of yesterday's presenters and discussion and I have to say it was really excellent and I just want to publically thank the presenters who came yesterday. They did a phenomenal job and also the commission members, who, as always, do a phenomenal job and I just have to comment before we begin on this phenomenal room with angles reading, no doubt not our previous reports, but we should be inspired by the angles above us and we aspire to make the angles smile with our report and my thanks to Dan Sulmasy for inviting us here. Dr. Sulmasy has a wonderful environment in which to work so may the spirit of that environment be with us. We are--I consulted yesterday with our executive director who is our designated federal officer makes this meeting official, Lisa Lee, and Jim Wagner to get me up to speed on where we are. I am eager for us to continue our discussion of the pediatric medical countermeasures question and what we are really going to focus on for the rest of the morning is our draft ethical framework to assess more than minimal risk pediatric research with no direct benefit to healthy participants, but significant benefit to children of whom the children are who would be tested and done research apart. I think it is very important for us to, and that came out yesterday, and it is very important for us to begin with the importance and I think Dr. Fleischman said it would … his recommendation, which comes from the earlier 404-406, we might consider using the term that the issue is of vital importance because that is the--we want to begin in our minds with the case that would bring us to this question, which is an issue of vital importance. So let me just say, just to get through the one specific for anybody in the audience at the registration table, out front, and any staff members have comment cards and we really do welcome you as you hear us deliberate, staff raise your--you may want to just take a card in case you are so moved to write down a comment or question and one of the staff members, Lisa Lee, will probably bring it up to us and Jim or I will read them aloud. We take very seriously our commitment to getting public feedback. We have gotten a significant amount of public feedback on this question. Let me before we begin do two things, ask everybody, members of the commission, to introduce themselves and then I want to ask Jim Wagner to say a few words and Dr. Sulmasy, why don't you begin.

DR. SULMASY: Dan Sulmasy from here at the University of Chicago Medical School and the Divinity School.

DR. GRADY: Christine Grady from the National Institutes of Health Clinical Center.

DR. MICHAEL: Nelson Michael from the Walter Reed Army Institute of Research.

DR. ATKINSON: Barbara Atkinson, Emeritus from the University of Kansas.

DR. KUCHERLAPATI: Raju Kucherlapati, Harvard Medical School.

DR. GARZA: Alex Garza, Department of Homeland Security.

MRS. ALI: Lonnie Ali, caregiver in Parkinson's research, Advocate.

DR. ARRAS: John Arras, University of Virginia.

DR. ALLEN: Anita Allen, University of Pennsylvania and its Law School and Philosophy Department.

DR. HAUSER: Stephen Hauser, University of California, San Francisco.

DR. FARAHANY: Nita Farahany, Duke University School of Law and Institute for Genome of Science and Policy.

DR. WAGNER: Jim Wagner at Emory and I want to welcome our chair back to the position. Indeed, we did keep the seat open yesterday. Many folks addressed it directly I think while we were all here (laughter). And I also want to thank the commissioners for their conversations yesterday, which I think are really going to inform what we are going to do today. My brief comments about the document, about the framework that we're putting together, is that it has helped me in reading it to look at issues from two perspectives. One is the perspective that is the cautionary perspective, which I think we're called to do, but I think we should understand also the prospect that this could be enabling document. This sort of document providing the kinds of terms under which we ensure that certain kinds of research can go forward to protect young people, to protect children, but go forward of course in a good way. We have one sentence in here that addresses that. It says that the framework is not meant to be an insuperable barrier. I would enjoy an opportunity just to reword that a little bit that it's not to be something negative. It is in fact to be something positive, if we craft this appropriately it seems to me, so I look forward to our conversations today and I am ready and happy to yield the gavel to our chair.

DR. GUTMANN: Thank you Jim. So I think we should go back to where we left off, in the afternoon, in the late afternoon session and go through with the questions that were raised in the late afternoon, the framework Under 407, the secretary of HHS informed by a national panel of experts, which would be determined for that particular question would determine whether a research study, and this is the language from 407, I should just read it to get us started. 1. The research presents a reasonable opportunity to further the understanding prevention or alleviation

of a serious problem affecting the health or welfare of children. 2. The research will be conducted in accordance with sound ethical principles. And 3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians. The reason we have been assigned a study, which we have been asked to conclude with recommendations, is that there is room to build here and we are not recommending new regulations as I understand it. And this came up yesterday, we are recommending a set of standards that would help a 407 group and help the Secretary specify these very broad standards better, especially one and two. The consent of children and the permission of their parents or guardians actually refers in the 407 to another set of quite specific guidelines. We may want to say some more about that, but really that isn't the primary challenge. The primary challenges are one and two. First, we can specify the type of problem that qualifies as sufficiently serious problem under section 407 and what qualifies as a reasonable opportunity to address it. Second, we can propose a rigorous set of ethical conditions that must be met to determine whether the research will be conducted in accordance with sound ethical principles and finally, we can reiterate the importance of parental permission and child assent. I would like to start by asking Christine to reflect back on the discussion that centered around subcommittee A's recommendations of yesterday and say where you think we are and where you think the open questions are and then we can have a broader discussion of that.

DR. GRADY: So one thing that you actually already mentioned Amy that I think came up yesterday, and is probably important for us to do right up front, and Raju brought it up yesterday too, is to recognize the importance of having safe and acceptable methods to protect children from possible terror threats or naturally occurring threats.

DR. GUTMANN: Can I--I am going to sort of pause to see whether, you know, I can look and see people nodding their heads, but not everyone nods their head. Does everybody basically agree that up front we should speak to the importance of developing such understanding in order to be able to treat children? Let me just stipulate, I am asking is it necessary? It is never going to be sufficient. The sufficiency is going to come after we go through all of the conditions, yeah.

DR. SULMASY: Yeah, I think this ties into some of the discussion yesterday about the, you know, the Kantian principles too and just starting there. Um, I am not sure in some ways that we really have to go further than sort of a restatement of Belmont principles really to think about this is where we want to go because I think that would capture some of what Raju was concerned about too to say that we want to help children, we want to protect them from harm, we want to respect them as persons and make sure they are treated justly, and there is a way in which all of those principles still are affecting all of our deliberations and that might avoid the trap of saying that we're really caught in Kantian language or utilitarian language.

DR. GUTMANN: Yeah. You're jumping, I mean that is okay, but I think it is jumping ahead of the particular, much more basic thing, but we can jump if you want.

DR. WAGNER: Before you jump, you were focused specifically on whether or not it is important for us to have a statement that we wish to promulgate or do our work in order that we can protect children from events, whether they are natural--

DR. GRADY: I think that is what I was suggesting, but even that could be controversial because, because of all that we have talked about in terms of not being about to know for sure, but there was I think pretty passionate testimony yesterday, and other times, about, you know, if there were to be an event, we should be prepared for it and one way to be prepared for it is to have safe and available ways to prevent and treat children and others.

DR. WAGNER: And so I would cast my vote also that we should do this right up front and this is, and this then the second issue, not secondary, but the second issue is the safety issue. I fear that if we don't focus that, that is our intent, our intent is to provide guidance for that kind of safety that we run the risk of imaging a process that would not let any risk run through the sieve and, of course, the only sieve that would not allow chaff to pass through it is a sieve that won't allow anything to pass through it and I think it is important to say up front that we intend to pass through this appropriate protocols that would help ensure the safety of children in the case of an event.

DR. GUTMANN: Raju.

DR. KUCHERLAPATI: Amy, I initiated this discussion yesterday and what I was saying, and also to respond to what Dan said, this is not about children getting into clinical trials or other types of testing. The notion that I am trying to say that it is important to be able to state is that as a nation, we have a responsibility for the health of all peoples, including children and that we should try to do everything as a nation to protect children's health and so that is just a preamble and part of the protection of health is what we're talking about in terms of medical countermeasures, but it is not the only thing, so it is a much bigger statement and that is what I wanted us to articulate that such a view.

DR. GUTMANN: Good.

DR. KUCHERLAPATI: And I think that, that--

DR. GUTMANN: Good. And you all agree that we have to state it in a way that it doesn't suggest that we can do everything no matter what the cost to individual children because that is the other horn of this dilemma and I think whatever we state--that is why I say necessary,

but not sufficient, a necessary condition is that we, as a nation, want to protect the wellbeing of children as a class of people and then it will be as long as in doing so, we abide by sound ethical, you know, other sound ethical principles. That is an ethical principle in itself to begin with.

DR. WAGNER: May I offer just two words to your point?

DR. GUTMANN: Okay, go ahead.

DR. WAGNER: Just help straighten my mind out, aren't we having a conversation about children as potential victims of some form of disaster versus children as subjects in some form of research and we want to protect them in both categories and does it bear saying up front something about the notion, we might not want to use the word victim, children as victim, and I think, yes, it does. That's the--that helps me keep separate these two things.

DR. GUTMANN: Yeah. Nita.

DR. FARAHANY: I understand Raju to be saying something slightly different, um, and correct me if I'm wrong Raju, but I had understood you to say not just a statement up front about how we are seeking to protect children and prescribing an ethical guideline by which we can do so, but that there is an imperative to protect children, which should guide us under certain circumstances to actually test and prepare in the events that there is some sort of, you know, event like anthrax or other type of action taken against the population, so it is a more positive statement saying there may in fact be an ethical duty to test under certain circumstances if the risk were high enough, if the, you know, and we would have to figure out what those are, but that it isn't just prescribe ethical guidelines for when that might happen, but we might in fact have a duty to do so. Is that right? So I think that is a little bit different.

DR. GUTMANN: You can, yeah, but you can only have a duty to do something if you're not violating another principle in doing it, so you can't have a duty to protect anybody if it entails torturing a child, at least not in the cases we are considering, which is not end of the world cases. So I would just be wary of stating anything up front just as I was wary of beginning with the children have rights of being tested in certain ways. We don't want to begin with a statement up front that basically decides issues, as opposed to opening our minds and any groups' minds to thinking about all of the steps that have to go through.

DR. FARAHANY: I agree and I think by saying under certain circumstances. It is a question of whether or not it's permissible versus an affirmative duty and you can say there is an affirmative duty to do so under circumstances, right, which ensure, etc., but I think, I think the idea that there is an affirmative duty as opposed to simply a permissible action--

DR. GUTMANN: Right.

DR. FARAHANY: That can be taken is a different framing and one that I am supportive of taking into account that we have to say under circumstances, including etc.

DR. GUTMANN: Another way of saying that is, and then I will go to Dan, is there is affirmative duty both to protect children as a class and to protect individual children from subjecting them to undo risk, both, and we are going to put a set of conditions that try to meet both of these and there are, so there is a sieve that it can go through. Dan.

DR. WAGNER: And that is important.

DR. SULMASY: That is part of why, um, I sort of immediately as you detected, jumped the gun because--

DR. GUTMANN: No, but you were--

DR. SULMASY: Because I, because I wanted to sort of say that up front, we have to say there is panoply of principles here that have to be taken into account and then it gets specified in the particulars of this of how does the duty to protect children from the harms of bioterrorism, epidemics, etc., get balanced out against the duty to protect them from potential exploitation or harms of research.

DR. GUTMANN: Good. Christine, you can proceed. We got you past one sentence.

DR. GRADY: That is good. It was an important sentence.

DR. GUTMANN: But we made progress didn't we?

DR. SULMASY: We don't have to go back there again.

DR. GUTMANN: Right.

DR. GRADY: I think it actually helps us with the next sentence to tell you the truth, so because in thinking about it that way that there is a sort of positive reason to be pursuing certain kinds of research, the emphasis on evaluating each proposed study to see if it is a reasonable opportunity to address the serious problem is the next thing that we need to tackle and I think, I mean, the 407 language says that, but we need to sort of think about what does it mean to be a reasonable opportunity and in many respects, to me, it is a critical part in the circumstances that allow us to go forward because we have to make some assessment about whether the proposed

research has the potential to answer a useful question that will further our understanding in some way of what we're trying to achieve, so reasonable opportunity is the next thing that we need to discuss and I think that is sort of the way that I've been thinking about it, that the proposal that is being reviewed has the potential to answer a useful question to further understand the particular serious problem that we are trying to understand or alleviate. I don't know if anybody wants to--

DR. WAGNER: Now that is in the text already is it not?

DR. GRADY: Yeah, I added a few words that aren't written there.

DR. GUTMANN: Are we now doing the broad 407 or are we doing a narrowing to medical countermeasures--pre-event medical countermeasures, because if the latter, I thought Alan Fleischman had a very useful suggestion, which John and others picked up on, which is to import, make use of the language that is used in 404-406 of if we are talking about more than minimal risk research that it should be of vital importance and this language, it is not like a constitution that--and we are not attempting to change the regulations, but this language is much fuzzier than saying, and much less compelling frankly, then saying that something is of vital importance, so I would, having read the transcripts, and I would suggest we try to bring in the language and our recommendations of vital importance.

DR. GRADY: I agree with that, but I think there is still a reasonable opportunity angle to this that needs to be flushed out a little bit.

DR. GUTMANN: Right, right. Absolutely. That wasn't--that doesn't obliterate that. Yes, John.

DR. ARRAS: Thank you Christine and the others. There could be a gap between the notion of a matter of vital importance and the notion of reasonable opportunity because one thing that has been troubling me is that, especially if we're talking about medical countermeasures, it would be very easy to, to make the case that this is a matter of vital importance, okay? But, it is something else again to say that the particular proposed protocol is a matter of vital importance.

DR. GUTMANN: Again, each one is necessary. Right?

DR. ARRAS: Yeah, because, you know--

DR. GUTMANN: They obliterate one another.

DR. ARRAS: In the case before us--

DR. GUTMANN: They don't obviate one another, sorry.

DR. ARRAS: In the case before us, you could, I mean, I am kind of sitting here wondering well, okay, this will give us a smidgeon of the evidence. It is not going to tell us whether this particular vaccine is safe or effective, which is what people usually want to know about a drug they are taking, so it is going to give us just one small step in that direction, which a lot of our panelists said, well, you know, it is better than nothing and you got to start somewhere.

DR. WAGNER: But that's not a reasonable opportunity, that gets back to reasonable opportunity.

DR. ARRAS: But that is what I am asking.

DR. GUTMANN: Good.

DR. WAGNER: Good point.

DR. GUTMANN: Barbara.

DR. ATKINSON: I would just say to that, it's a vital step though and I think it is the first step in anything, so it would fit my definition--

DR. ARRAS: Okay. Well yeah, yeah, yeah.

DR. ATKINSON: And I was going to suggest that, that needed to be added, but I wanted to go back to the broader issue of what this document might be and to me I would like to see it be a framework for any kind of pediatric research to the extent that we can make it that and not just medical countermeasures because as I looked at what were 407, any kind of pediatric research that would fall in the 407 category, as I looked at the list of things that had already been brought to the Secretary, most of them were not medical countermeasure issues and I think they need the same guidance and the same sound ethical principles there and this document doesn't seem to me to be that far off what you would expect everything to be, so in the broadest sense, I would like to see if fit for all 407.

DR. GUTMANN: I think if we get these principles right, which we will, they will be relevant to any 407 case and for any 407 case, there is inadequate guidance in the language that exists right now, which is something that I think 407 panels have been struggling with. Dan.

DR. SULMASY: I was going to ask Christine, it sounds like you want us to specify though what might be meant by reasonable opportunity and I just would be curious about any

discussion from anybody about what might constitute filling that out because I am not sure I have an a priori idea of what reasonable opportunity means, other than just opportunity.

DR. GUTMANN: So subcommittee A did some work on this, right? A little bit.

DR. GRADY: Very little actually.

DR. GUTMANN: Give us your views Christine.

DR. GRADY: Let me just say that it may be hard to specify because the devil is in the details of a proposal, but I think it is an important part of the framework and I would like to have it emphasized as such because some of the discussion that we have had over the different meetings that we've had, you know, people understandably say we need medical countermeasures for kids, we need to be able to protect kids, but that doesn't mean every research project is going to get us there and so that is the kind of balance that I think needs to be paid attention to by the people who apply this framework to a particular study and so maybe, maybe it doesn't need further specification, but it needs emphasis or something to say that some--the details of the study will determine whether or not it is a reasonable opportunity to understand going forward. Does that make sense?

DR. WAGNER: Do you think the language does that Christine? Where are you reading? Reasonable opportunity to further the understanding prevention and alleviation.

DR. GRADY: It might do it, but we almost left it out of our discussions.

DR. WAGNER: What would you suggest?

DR. GRADY: Um.

DR. GUTMANN: Well, here is a for example, the problem being addressed must be one for which the current state of science has the potential to provide answers and for which there is a specific candidate available for testing in children and that there is no less risky potential available, otherwise we wouldn't be considering the more risky one. Alex.

DR. GARZA: I am having a hard time struggling with this too Christine, but I think you're on the right track with this language, so the reasonable opportunity to me says something is this--does this make logical sense that we should be doing this? Is a pragmatic? Is there enough to tilt the scales to--yes this, seems like something we should be exploring. The phrase of vital importance though I almost think deserves to be underneath the serious problem context rather than reasonable opportunity.

DR. GUTMANN: That is what I was suggesting. I was suggesting the serious problem is a problem of vital importance when you are speaking about more than minimal risk testing on children. If it is less than minimal risk, I don't think it has to rise to the level of vital importance. I am saying I don't think so, but I am really extrapolating from a very large body that precedes 407 and, therefore, as we had agreed we're extending the framework rather than inventing our own from scratch. Dan.

DR. SULMASY: I was just going to ask Christine, if you draw the distinction between the opportunity to conduct a research project, which I think is some of what Alex was suggesting, which might be even a field experiment because of some natural event that occurs and then the sort of qualities of the protocol that will take adequate advantage of that opportunity because that is part of what subcommittee B was doing was sort of saying, what are the conditions under which the research project would be sufficient to take adequate advantage of that opportunity to be able to justify it, so maybe those are actually separate concepts.

DR. SULMASY: They are sort of distinguishable at least in theory, although in practice, you are going to see a protocol in the face of an opportunity, so you have got to take both into account simultaneously, but maybe this language is distinguishing the opportunity to do the research from the protocol that will take adequate advantage of that opportunity so that it becomes morally permissible to put children at risk in order to conduct it.

DR. GUTMANN: Okay. Can we go on to the, um, clarification of the threat and probability of exposure, which Nita brought up? Um, the probability or threat of exposure, this dimension includes the threat of an attack or the likelihood of a naturally occurring outbreak and the vulnerability of exposure of children should such an attack occur, um, and we now are using a, you know, a problem of vital importance and I guess the question that I would pose in the spirit of what Nita was asking is if we stipulate that this has to be a problem of vital importance, should we leave it open to the 407 panel and the Secretary to say why she and they believe that it is of vital importance rather than trying to devise an algorithm ourselves of medium to high risk times harm and we could actually say that it ought to be the responsibility of the Secretary and the 407 panel to indicate why they think this is a problem of vital importance. I think to come up with us, what Nita flagged, for us to come up with the algorithm will not cover, as Barbara said we should try to and Raju I think has been urging us, will not cover all the cases because we can't imagine all the cases that might come up. I see a lot of nods. Is that--so I think instead of trying to define the probability of risk, where probability means the probability that it would happen, we should ask the 407 panel and the Secretary to make clear why they deem this of vital importance. Okay.

DR. FARAHANY: Just one--

DR. GUTMANN: No, please.

DR. FARAHANY: Comment on that, which I is think that is great as a way to move forward on this. I think it would be okay for us to specify things that we think could satisfy that.

DR. GUTMANN: Right.

DR. FARAHANY: And it could be things that are high magnitude and low risk. It could be things that are high risk and medium magnitude, you know, it could be we can specify a set of stipulations as to things that we think could, under certain circumstances, be justified just to provide guidance, but that we think ultimately this should be a determination that is left to, you know, the situation and the Secretary.

DR. GUTMANN: Right, so I think that, I think that is a very helpful addendum. I think we should give examples and clear examples, not borderline ones, clear examples again in the spirit we are doing this because if something is above the bar, the health of children is at risk and children, all children, including those who would be tested stand to benefit, we should give some clear examples of some of hypotheticals because we don't have, real examples are always messier, clear examples of why. For example, a 407 and Secretary could deem a vital importance, okay? And we should avoid the hard cases here because hard cases make bad recommendations in this particular case.

DR. GARZA: So, Amy, I just want to sure that I understand correctly what we are agreeing to. So does this mean that we are going to come up with different language under 2B, under the probability?

DR. GUTMANN: Yeah.

DR. GARZA: Okay.

DR. GUTMANN: I think we are going to avoid saying it is a necessary condition for something to be X probability of risk because the language that we tried, which was low, medium, high, is very vague. I mean what is a low probability when it's just too hard. You've convinced me and others have as well and I think we are all nodding here that we don't have the algorithm here and I don't know that anybody has it, but we might as well do this as a case, we give the guidelines and then the people who are dealing with the actual cases make the case and have to make the case, so they will have the burden of making the case, but it will be case with a real--they will have the real empirical knowledge that we don't have.

DR. GARZA: Right. I agree.

DR. WAGNER: So how will this read?

DR. GUTMANN: Well, we are not going to draft--

DR. WAGNER: No, no, no.

DR. GUTMANN: I don't want to draft.

DR. WAGNER: But is it simply saying that we still believe probability exposure is a factor?

DR. GUTMANN: Yes.

DR. WAGNER: So it is not like we are striking these?

DR. GUTMANN: No, we are not.

DR. WAGNER: And what we are saying is that probability is a factor and its vital importance is to be determined by the Secretary?

DR. GUTMANN: Right, we will say that all of these, that the degree of harm and the probability of it happening, of the incident or attack, let's just call it an incident because it's--the probability of the incident and the degree of harm are two of, two essential conditions to determining whether something, research is of vital importance and we recommend, and again I am not drafting this, but we recommend that the Secretary ask the 407 panel to give her enough reasons and information that they would deem this of vital importance because of the probability and the degree of harm. And the higher probability and the higher degree of harm, the more something is of vital importance.

DR. GARZA: Sure. I just want to put this out there to make sure that--the probability of anticipating event is, the probability comes from usually Gaussian statistics, right? You have a history, so you can predict or you can come up with a reasonable model to predict. The reason why these events are such big deals is because they are unpredictable, so we never predicted H1N1, we didn't predict SARS, we didn't predict Amerithrax, we didn't predict any of these things, yet they still happened and so, to me, this notion of probability is very difficult because we are using probability from a very statistical point of view instead of where we usually work for, from, which is the position of could it happen, not the probability.

DR. GUTMANN: Alex, I hear you and I really thought about this a lot as I am sure other people have, it is, um, and there, there, that something just could happen is not going to be enough to justify--

DR. GARZA: And I understand what you are saying, but I think, I don't think they are mutually exclusive and so, I think this is where the risk sort of picture comes in more so than the probability because if we are basing it off pure probability, I can tell you from and, you know, I know the most of anybody in this room about the probability of these things happening and so there is never going to be a pin point accuracy on probability, right?

DR. GUTMANN: But that's what--

DR. GARZA: And so to make it a condition, I think is going to be very, very difficult because if we knew exact probability, we would take care of it before it even came to the light of day, right? So, and, then, so what are talking about is after the fact mostly because--then we can say well, it happened.

DR. GUTMANN: So, Alex, we don't know the exact probability of the weather and the weather--

DR. GARZA: But we have a much better idea of the weather than we do of this.

DR. GUTMANN: That is what I was just about to say was much better idea and I think, you know, Nate Silver's book, The Signal and the Noise, which just came out, is very good on probabilities and on the really difficulty of dynamic, the problem when they are dynamic, they are non-linear and they expand on each other. I still think what we have said, which is that we need to ask the Secretary and the 407 panel to state why they believe this is of vital importance on the basis of probability and harm is going to be important.

DR. FARAHANY: Can I suggest a potential friendly amendment and Alex, see if this works, which is, it sounds like you are saying it shouldn't be an absolute bar, right, that a consideration of vital importance, we are going to be able--

DR. GARZA: I think there is no way you will get above the bar if--

DR. FARAHANY: Well, right. So what if, what if it is factors that we think are important in consideration, right, because ultimately what we care about is the determination of vital importance, factors that we think are important in doing so are, you know, the plausibility of the risk, the probability of the risk, the, you know, the degree of harm that is expected, so

these are factors and consideration, but not absolute bars to being able to determine something is of vital importance. Is that something that's--

DR. GUTMANN: Yeah, except I would, I, I, this is the one thing that being--there are so many ways in which the world could come to an end-let me--right? There are, and which ones we protect, we will subject children to above minimal risk for has got to depend in part on the judgment of what the probability that the world will come to an end in this way is if we don't do something. I don't think Alex is disagreeing with that, but what Alex is saying is there, there are confidence intervals--

DR. GARZA: And they are very wide.

DR. GUTMANN: And I mean, you know, so I put my statistician/mathematics hat--there are confidence intervals here, so we need confidence intervals then. We have, you know, but we are not going to stipulate those, it is just that we can't open it so that somebody could say--

DR. GARZA: No, I agree.

DR. GUTMANN: Subject children to more than minimal risk even though we don't have a clue.

DR. FARAHANY: But that is not saying we don't have a clue, right, to be able to say--

DR. GUTMANN: That is all I am saying, that we have to say more than that.

DR. FARAHANY: Well, but, so take the, take the example of anthrax, which is that we know it is number one on the list, but we don't have any estimate as to what the probability is, right, so we know it is considered a high risk item, but we can't actually--

DR. GARZA: But so we build probability into our risk assessment in many different ways and most of it is based off of--

DR. GUTMANN: How do they know it is number one on the risk because you think the probability is higher than a lot of other things.

DR. GARZA: So there is physical characteristics of the agent, which makes it somewhat easier to produce than other things, easier to weaponize, things like that, but there is also you have the, um, the input from the intelligence community, which really is where it starts out from the intelligence community that says what do we think are the probabilities that somebody would

do something bad using this particular thing and that is how we build the risk model, so but I can't give you, but that probability is going to be very wide.

DR. GUTMANN: We are not asking for a number, a probability number, we are asking for a judgment of how high the probability is and that's what--and we not asking for it as a commission, we are saying, us, right now, on any--we are saying a 407 panel and the Secretary should be able to state why this is of vital importance--

DR. GARZA: So if that probability was built into the risk model, where we could say, this really should be determinant on risk rather probability because probability is part of the risk model then would that satisfy it?

DR. WAGNER: And that is typical risk management mathematics.

DR. GUTMANN: As long as it can be made clear.

DR. GARZA: Okay.

DR. WAGNER: Is that okay? Do we know where we landed on this?

DR GARZA: I think we will have to work with the drafting of the language and stuff. We are not in disagreement, we are just different ways of presenting it maybe.

DR. GUTMANN: Raju.

DR. KUCHERLAPATI: I think Alex is saying that probability is not always knowable and that if you stipulate that you have to determine the probability and the decisions are going to be based upon some number of probability, you may not be able to get there and I agree with Alex and so it is that I don't think that it is possible. I think the general language that we talked about of, you know, earlier, you know, probability versus the impact of something like that happening and combinations of them, I think that could be qualitative and that should be okay and like in the case of anthrax that we have heard, for example, if a person is infected that there is a 75% chance that, that person will die from it. That is a very clear number. That is a very high impact if that happens, right? And so I don't know what the probability that there would be an anthrax attack, but that number states that this is sufficiently important that we need to do something.

DR. GUTMANN: No, that--can I just say that how you just put that cannot be correct. That is you have to--that is what is correct is that the fact that anthrax, if it happens, would be enormously destructive is important, but if it weren't number one on the list, if it were at the

bottom of the list of risks then we would not--that would be, it would put it in different category then if it is number one on the list, so that is why I said we don't need an algorithm, we are not going to state an algorithm here, but making the case that this is of vital importance is a combination of harm and, you may not want to call it probability, but likelihood, okay, because there are huge harms with such remote likelihoods that we are not going to go ahead and do more than minimal risk testing and I think we all agree, so Raju, I don't think you disagree with this, it is just that you can't say that it is just the harm. It has got to also be some understanding of the likelihood.

DR. KUCHERLAPATI: Amy, I understand, but whether something is number one or number five or number 10, that doesn't diminish the importance of it, so I understand what you're saying that number one is obviously more important, but, I, you know--

DR. ARRAS: Are you talking in terms of probability or the degree of harm?

DR. KUCHERLAPATI: No, no, this is not about, you know, Amy was talking about whether, you know, whether anthrax is the top of the list of concerns, you know, for the government. If that is not the case, you say you would think about it differently and I am saying that it is not just, you know, where in the list of things there is something, but how important is it and I guess what I am arguing is there may be other sorts of disorders, if they have similar types of features, for example, Yersina or something like that, could equally be important and that may not be at the top of the list, but it would be devastating if it happened.

DR. GUTMANN: Just to clarify, I wasn't saying it had to be at the top of the list. I was using that as an example of an estimate of its threat, not just in the magnitude and Alex is agreeing with me, not just in the magnitude, but how easy it would be and, therefore, how likely it would be that this is an actual threat compared to something that if it happened would be devastating, but the likelihood of it happening is, not only totally unknown, but it is remote.

DR. GARZA: Right, so maybe I can put this into context, so we look for many different pathogens around the country in various different ways and we can't look for everything, right, and so we rely on our threat and risk assessments to guide us and these are the things that we should be looking for and developing our own, not countermeasures, but, um, um, equipment to detect and we have to base it on something, and so we use that something as our risk assessment and I appreciate the word, I think, likelihood much more than probability.

DR. GUTMANN: Good. That is a friendly amendment actually, likelihood, because it doesn't call for number. Yep. Very good. Dan.

DR. SULMASY: I was precisely going to endorse that, the risk being a little more philosophical here. Ian Hacking actually distinguishes between frequency type probabilities, which are measureable about events out in the world, which can have confidence intervals because we've done the studies and belief type probabilities, which are statements about our belief about for instance what might happen in the future. We use the word probability to cover both of those quite often, but it is ambiguous and here, I think we are conflating frequency type probability and we don't have any frequency type probabilities to talk about in this case. We only have, we only have estimates of our belief about the future based on whatever evidence we have and so the word likelihood I think might be serviceable in talking about that. For instance, nobody is going to subject children to a study about genetically engineered rhino virus that is going to be lethal to people because we think it is very unlikely that somebody is going to do that, so there is some sense of likelihood that needs to be built into it, but probably the word probability, given its ambiguity, is causing the trouble here.

DR. GUTMANN: So there has to be, as Jim just, a vital risk, which is, um, a combination of the harm and the likelihood. Okay. We are going to move on. May we move on because I think we have exhausted this one? Okay. Next is--

DR. ARRAS: Should we change our flights?

DR. GUTMANN: No, no (laughter), we are fine. We're fine. Propose--I have to vote, so (laughter). That is an ethical duty too. Propose a rigorous set of ethical conditions. We have the threshold, we, um, all of you thank you, Nita for do that. Groups struggle with defining quantifying risk. We have dealt with that. We are not going to try to quantify it. Scientific validity and ethical research.

DR. FARAHANY: Oh wait, Amy, there was one before that.

DR. GUTMANN: Okay. Sorry. Go ahead.

DR. FARAHANY: It is just a statement.

DR. GUTMANN: What page are you on?

DR. FARAHANY: I am on page 3 under 1, the second paragraph, the second full paragraph about half way down, we have such research may only proceed when without any children as a class would remain vulnerable to the possible serious harm and only by going forward with the research, the potential for serious harm would be mitigated. So that sentence, I worry about just because I am imaging, you know, there are potential alternatives that we could imagine. There are other things that could be developed along time, so I wasn't sure what we

meant by this sentence. It seemed to be put to a kind of absolute bar to the ability for research to proceed, so I would say this is something we strike or that we need to modify saying that, you know, we expect that by going forward with the research, the potential for serious harm would be mitigated, but not only by going forward.

DR. GUTMANN: Yeah. I think -- Yeah, yeah. Okay. Okay.

DR. GRADY: Can I just say Alan Fleischman said something yesterday, which might also be another way to think about that sentence, something like research, such research should proceed when failure to include children in research will leave them susceptible to risks that exceed the risks of research. That may be too complicated, but that is the idea.

DR. GUTMANN: It's a good--that's--I would say that--

DR. WAGNER: It's an affirmative way to say it too.

DR. GUTMANN: I would say that is another way of saying it that makes--

DR. GRADY: Sense.

DR. GUTMANN: I think that we can use both ways actually. In other words, that is fine. I think that is good.

DR. WAGNER: I like the tone of it too.

DR. GUTMANN: Okay.

DR. ARRAS: We are talking about different classes of children though, right? Well, I mean, I understood this conversation to say that, you know, if you don't do the research, you will be subjecting children, you know, to a high risk of harm than you would the children in the research. Is that correct, that formulation?

DR. GRADY: That is sort of the way we did it, yeah. Failure to include children would leave children as a class more susceptible.

DR. ARRAS: I just want to underscore that we are talking about children as a class and not about particular children.

DR. WAGNER: Failure to include particular children would lead children as a class I guess.

DR. GUTMANN: Yeah. So that condition does not speak to how high a level of risk you would be willing, we should as a society be willing to subject any child to. It speaks to something different. Go ahead John.

DR. ARRAS: Yeah, no, it is just that I am very suspicious of attempts to sort of bring in the back door direct benefit to children in these kinds of studies. There have been a few attempts at that.

DR. GUTMANN: Can I say something about not, about the broad, um, this is not a case and we are not going to try to bring in the back door, it is not direct benefit to individual children; however, I do think we have to avoid bending, what I would consider bending over backwards and we need to say that this is a case of where the children who are being tested are part of the class of children who stand to be benefited because, and the reason why this is so important, I think we also have to say in the report, we are not considering nor do we recommend that our society ever consider testing children for the benefit of adults. There really is embedded in this framework a very important principle and I think it is a principle that can be stated, and I say this for, I read Anita Allen, in a variety, in a pluralistic number of ways of convergence, of ethical outlooks that we are talking about setting some ceiling on the risk that you would have children subjected to for the benefit of the class in which they are in, which is children and we are accepting, indeed reinforcing the line that we would not have children tested for the benefit of others, that is other than children. So that does mean, and I mean, let me just give you the philosopher's example of that. You could use children, and some societies do, for fighting wars in ways that, and you would protect the society, in ways that you couldn't use adults. Suppose, and this would be, suppose there was a way in which you could use, you needed somebody who is really little and innocent looking to get some information, we as a society would never do that and these, um, recommendations we are making are accepting that there is a class of which the individual children are apart that stands to benefit and these individual children will benefit too as part of that class, but it is indirect because we are not doing it for them specifically.

DR. ARRAS: Yeah, a case closer to home, Amy, that drives home a point is Willowbrook.

DR. GUTMANN: Exactly.

DR. ARRAS: It is a controversial case and people still debate it, but one of the major criticisms of that Willowbrook State School experiment was that they used children in a mental institution to find out, you know, the identity of hepatitis B.

DR. GUTMANN: Which they could never benefit from.

DR. ARRAS: And a lot of people said that they have should have used adults to do that, so.

DR. GUTMANN: So, it is a significant, I will call on you in a second Raju, it is a significant ethical principle that the children who would be tested would be among those who stand to benefit. It is still not direct, but it is significant, otherwise we would be considering testing children for things that they would not stand to benefit from. Raju.

DR. KUCHERLAPATI: I thought that John was sort of bringing in another aspect that is actually very important for us to consider. 25% of the US population is children, so that is approximately 75 million children, and one concept that we haven't talked about is that we are concerned and much of this discussion is based upon the 200-400 children that will be in a part of this medical countermeasure study and that whatever harms that today that, that study might engender, whether it has to be considered in the context of what we would be doing for the 75 million children. In other words, if you don't do this study, what is the kind of risk that you are putting the 75 million children in and whether we should weigh that in some fashion.

DR. GUTMANN: Dan.

DR. SULMASY: Just to try to generalize that principle beyond even just children, I think it might be useful to say it more as something like vulnerable subjects can be recruited into research trials if the benefit accrues to members of the class that makes them vulnerable in the first place and can't be studied without recruiting such vulnerable individuals and I think that was an important part, the last part that Alan said, that if you can help the children by studying adults, you ought to study the adults.

DR. GUTMANN: Yeah.

DR. WAGNER: I actually prefer that to the earlier.

DR. GUTMANN: Yeah, yeah. Good.

DR. ARRAS: Dan, can I just interject, mean, I agree with everything that you just said, but Amy, I want to press you a little bit on exactly what you mean by the sorts of benefits these children being researched on will get. You describe it as indirect, but what exactly do you mean?

DR. GUTMANN: Well, what I mean is that if we are testing children with above minimal risk procedures, they should be within the class of individuals who stand to benefit from the results of that research.

DR. WAGNER: The class of individuals who are among the vulnerable, I think, because it is possible, is it not, that we could be doing research on affected children post-event--

DR. GUTMANN: We are talking about pre-event.

DR. WAGNER: Yeah. Are we or are we talking about a broad construct for pediatric research? My concern is I imagine, if you give me enough time, that I can think of a situation where this would be a child that is in a larger class of vulnerable children, but there is a protocol or there is something that we will learn that may not directly affect them, particularly for just, you know, doing first stages of studies that may not pan out for years to come. Do you see what I am saying? I like the vulnerability.

DR. ARRAS: You are still fishing for the nature of the benefit, other than just happening to be in the same class.

DR. FARAHANY: Do we mean by class just children, right, so suppose we are testing on adolescences who are going to age out and be part of the adult population--

DR. WAGNER: Before they can benefit.

DR. FARAHANY: Right, but by saying of the class, at the time, I assume that is time bound, right, which is if there were benefits that were reaped immediately, they are part of that class, but simply we are ensuring that we are testing on the class that is designed to benefit from the research, even if they age out. It is a time specific thing.

DR. GUTMANN: They age out into adults and they will be benefited because we have an adult--we have protection for adults. Adults age out by dying, so you know.

DR. FARAHANY: No, no, no. I know. (Laughter). I am just saying it doesn't matter that the people may age out before they enjoy the benefits of it because we are talking about at the time class, so it is a time bound construct, not an unlimited time concept.

DR. GUTMANN: Yes.

DR. FARAHANY: So that solves the kind of concern that we might have from it.

DR. ARRAS: Yeah.

DR. GUTMANN: Okay. Scientific Validity and Ethical Research Design. Um. We have the proposed research in a pediatric population is necessary in order to achieve an important scientific, we have a vital, we've already changed some of that language and then tested in adults where an adult formulation is appropriate. The intervention has been thoroughly and safely tested in adult populations with regard to the same issues that would be studied with children. This means as well that when child participants become adults, tested MCMs will be available to them so for discussion, we should clarify that expected benefits include more than just therapeutic benefits and might be things like improved compliance, practicality, ease of distribution, etc. Okay.

DR. WAGNER: Did you miss … did we miss one more? I'm sorry. Stipulative language piece. On the bottom of page five, I have--

DR. GUTMANN: Well, we have different page numbers. You have your iPad.

DR. WAGNER: Oh, there it is right there.

DR. GUTMANN: We already did that. The quantifying risk. We already did that. We talked about that.

DR. WAGNER: Okay. Okay. Good.

DR. GUTMANN: We talked about that at great length. Okay. Um. That we are not quantifying risk. Are you okay with that?

DR. SULMASY: Yeah, no, perfectly. I just want to make sure again from, I think Nita did raise questions, which I think are reasonable, but they come up later about the risks to the, um, you know, of harm to the associated with the research protocol itself and make sure that we--because the same considerations don't apply to both, right. So there was another section--

DR. GUTMANN: We are not there yet.

DR. SULMASY: Oh, we're not there yet?

DR. GUTMANN: Okay. So some of you are pulling me back. We are getting there. We are going to get there. I think we are going to get through this. Um. The--okay. So the next, we've got expected benefit to children as a class, ethical research design, scientific validity

and so on, minimization of risks to children, fair subject selection, selection of scientifically and ethically valid research sites, okay. And then, the next--

DR. ARRAS: Can I make a comment?

DR. GUTMANN: Sure.

DR. ARRAS: On ethical research design. Would that be a good place to insert language about older children first?

DR. WAGNER: We did have that conversation stratifying the protocols to address older children.

DR. GUTMANN: And that was very well done yesterday and we spoke about that earlier. I think we are in complete agreement that given the scientific issue with regard to safety and immunogenicity, you work down the age groups, so if you have tested on 18 year olds, you begin with 16-17, and it can move, as yesterday we heard quite quickly, as long as safety and immunogenicity works. Okay?

DR. HAUSER: Under the, um--

DR. GUTMANN: Go ahead.

DR. HAUSER: Sorry

DR. GUTMANN: Yeah, Steve, go ahead.

DR. HAUSER: Expected benefit to children as a class, yesterday, we discussed the possibility of adding and/or practicality of use.

DR. FARAHANY: Right, so compliance.

DR. GUTMANN: Where is that? That does not impose greater than minimal risk without the prospect of direct benefit. Where are you looking, Steve?

DR. HAUSER: Bullet, sorry, bullet 3, under 2.3.

DR. GUTMANN: Yeah, that is the one I have, expected benefit to children as a class … so.

DR. HAUSER: And/or practicality of use.

DR. WAGNER: At the end of that sentence.

DR. HAUSER: Right after class. So the practicality must be--

DR. GUTMANN: Expected benefit to children as a class. It doesn't--I can't understand it. And/or practicality of use.

DR. HAUSER: Well, perhaps it should be at the end then, but the point is that the--

DR. GUTMANN: Yeah, why don't you tell us what the point is and we can draft it then. Okay, so what is the point, Steve?

DR. HAUSER: So the point is that the therapy must be, it could be in advance in a more practical way to deliver a benefit to children.

DR. GUTMANN: Okay. Okay. So--

DR. HAUSER: And we heard some--

DR. GUTMANN: That would be part of the expected benefit to children may be--

DR. HAUSER: One could say it is subsumed under benefit.

DR. GUTMANN: But we could clarify that the expected benefit to children could be a protection that doesn't exist or it could be a more practical effective and efficient way of--yeah. Absolutely. That could be added.

DR. ARRAS: Benji Freedman has a really nice way to put this. He talks about a portmanteau conception of benefit, not just mortality figures, but ease of use, all those things.

DR. GUTMANN: Which have a big effect on vitality, so that is a very friendly amendment. So where I have bolded for discussion from yesterday is post-trial requirements to ensure ethical treatment of children and their families, the ethical necessity of not treating children as means only, demands, accommodations to be made following the research for both participants and all children. We don't--we don't want the Kantian baggage. I mean it is basically ways of treating children so that they are being treated--there are different ways of putting it, so they are not being subjected to undo risk, so they are being treated as not as means only. In other words, the reason this language can be separated and we can use different

language and lots of different--from the whole baggage of any, um, one theory is that as a society where, and all of these regulations are looking at how to benefit children in a way that requires us to do research on children, but also sets some kind of a ceiling above which we would not subject individual children because they would be used not as, you know, they would not be respected as individuals, so we can work with multiple languages to express that. Um. And then the question, the substantial question here, is, um, the question of undue inducements, right? On the one hand, we want--I see this as kind of the Scylla and Charybdis. On the one hand, we don't want undue inducements to participate. On the other hand, we want the children who did, were volunteered, or did volunteer to be among those who benefit in the case of benefits, otherwise we are basically just using them and benefiting others when we could benefit them. So, we've got to figure out a way of, um, navigating this. Nita.

DR. FARAHANY: So I agree. I had raised the question about really just the way that we were wording it more than anything. So I think I agree that certainly they shouldn't be disadvantaged, certainly they should be prioritized where it makes sense and we have one piece of language here, which gets to that, which is if they stand in need of it.

DR. GUTMANN: Perfect.

DR. FARAHANY: I think it is important to highlight what we mean by that, which is, you know, if you, in a post-event world, if they don't stand in need of it because there is some other place in the country, which is actually the prioritized place, there are other priorities that can be taken into account, so what we mean by that is simply if they are in harm's way, they should directly benefit from the research because they participated. If they are not, they shouldn't necessarily be prioritized.

DR. GUTMANN: I think that is a very friendly amendment, if they stand in need of it, absolutely. Good. That is really helpful.

DR. WAGNER: And we do have that below right?

DR. FARAHANY: We have that already.

DR. WAGNER: Distribution to children if needed.

DR. FARAHANY: We just need to clarify what we mean by that.

DR. GUTMANN: We need to clarify and I think we need to bring it up. Barbara.

DR. ATKINSON: (Inaudible)

DR. GUTMANN: Okay.

DR. ATKINSON: (Inaudible).

DR. GUTMANN: Can you put your mic on?

DR. ATKINSON: Sorry. I have another category that could go in this one or perhaps in the last one, scientific validity one, but I think we heard a lot of testimony yesterday about needing an arm of the protocol that was a post-exposure that if there were an incident, you would have a planned outcome arm of the study and to me, it either goes in the post-trial requirements or it goes in the, the scientific validity section, but we need to say that we would at least encourage any proposal like this to have that arm of a study pre-planned.

DR. FARAHANY: Do you mean like what we talked about yesterday with the IRB approval, like have IRB approval?

DR. ATKINSON: Yes, have it all ready and ready to go and know what you are going to do to find out if, if it was either helpful or if it--what the next phase of the study would be if there were an episode that happened.

DR. GUTMANN: Yeah, I think that is very important because if we go back to something being of vital importance and are doing this pre-event, it would be wrong not to do what you can do to plan to carry this through post-event. It would be not only wrong, I would start with it being wrong, it would be a major blot on our government to have done this pre-event and not done everything you can do pre-event to make sure it is carried through afterward. I don't think anyone would, you know, would want to do that, but I think in our recommendations, we should make that very explicit because in the history of this country, we have had glorious events of preparing and then inglorious ones of not preparing.

DR. FARAHANY: I think Barbara was also referring to a separate post-event study though, right?

DR. GUTMANN: Yes.

DR. FARAHANY: If we also--if we expect that there will be post-event studies to recommend there be protocols that are submitted pre-event--

DR. GUTMANN: No, I took you to be meaning that.

DR. ATKINSON: Because that is exactly what I meant.

DR. GUTMANN: On the shelf, absolutely. Anita.

DR. ALLEN: We had some interesting conversations yesterday about community engagement and one thing that strikes me that we might want to do is to think about the post-trial moment as a time to sort of circle back to the communities about what we learned from the research and it may be kind of another way of showing ethical regard for the families and for the participants to let them know what we learned and let them know the implication of what we learned are going to be for their communities, if anything. Maybe we learn very little, but maybe we learn something important.

DR. GUTMANN: Good.

DR. ALLEN: So, not just making sure that the children who participated are going to be among those who benefit and are prioritized, but also to just kind of let people know what the consequences of their sacrifices have been, I am not quite sure how to phase this, but it just seems to me that before we get to the accountability section, there is also something right here that we need to say about the information.

Dr. GUTMANN: Yeah, I think after the break we are going to do--talk about the engaging communities, which after yesterday's and think about it, it has become more and more important to the legitimacy of the whole enterprise and I think Anita's point is very important, which is in the event of needing this, it is just as important to engage communities to see how--what made possible being this preparation and getting their feedback. Now, you don't do it at the height of an emergency, but as it subsides, it can be very important to get feedback and also to teach.

DR. WAGNER: Christine has a comment.

DR. GUTMANN: Okay. Christine, and then we'll take a break. Christine, you began this and you will conclude it and then we'll take a 15 minute break.

DR. GRADY: I actually understood Anita to say something in addition to what you just said and I don't know if it is right, but there is reason to circle back with the community of people who participated in the research to tell them what we learned from the research, even if there is no event.

DR. ALLEN: Precisely.

DR. GUTMANN: Oh, okay, good. Sorry, I missed that, and I agree with that too. I agree with that too.

DR. ALLEN: I was emphasizing what Christine said.

DR. GUTMANN: Excellent. We are going to take a 15 minute break and we are going to come back to transparency and accountability we are going to begin with. Okay. Thanks very much. Back at 10:30.