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for the Study of Bioethical Issues

TRANSCRIPT

Member Discussion

Meeting 12, Opening Remarks and Session 5

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DR. GUTMANN: Good morning, everybody, I'm Amy Gutmann. I'm President of the University of Pennsylvania and Chair of the Presidential Commission for the Study of Bioethical Issues, and I welcome you all here to day two of our 12th meeting of this Commission and happy to do so on behalf of myself and Vice Chair of the Commission and President of Emory University, President Jim Wagner.

We're going to continue our discussion of the pediatric medical countermeasure project going over some of the points of emphasis in the report, some of the issues that came up yesterday and I've collected a short list of those -- or not so short list, but I think they're ones in which we've, with all but one exception, we've spoken about in earlier meetings, but I think given that this is our last meeting on the topic, I thought it would be good to confirm where the Commission stands and get any reaction, other details on some of these points. And then I will turn the discussion over to be led by Jim Wagner to discuss future topics for Commission consideration. Let me just remind everybody here that we have cards, both at the registration, out front, and staff, why don't you raise your hands, have cards. Please don't hesitate to write any comments or questions on the cards and you can even write briefly and we can pass them up, a staff member will pass them up and we will read them.

Jim, do you want to say anything? Okay, let's get going. Okay.

So let me -- I want to start more or less where we left off yesterday discussing ethical considerations associated with pre-event pediatric medical countermeasure research and I really, rather than go over the ground, since we gave a narrative yesterday, I thought I would just do a list and I'll stop to see nods of head or elaboration on each part of this list of points that Dennis Thompson and Tom Beauchamp brought up, I'm not going to go over every one because some of the things we are just pretty clear or others we just can't go over in the report. But there are many that I think are important for us to just recognize and affirm, and some are more challenging for us to do some more work before we finalize the report. So, in no particular order:

One, we are going to recommend that there must be in place a plan, a specific plan for compensation for injury for subjects in research, where medical countermeasure research, the research being of the nature which we have emphasized throughout, which what makes this so special, that this is research on children who don't stand to directly benefit. So that I think is clear.

Number two, which we spent more time on in our deliberations, and I think it's worth saying something more here because Tom Beauchamp and Dennis both brought this up, is that we are recommending that a research protocol engage in what we call age de-escalation studies. And, for a particular reason. For many purposes, and let me just elaborate on that as we will do in more refined language in the report. For many reasons, for legal and ethical purposes, there is a bright line when a child becomes an adult. You have to pick an age, and it's 18. And so, when a child goes into an emergency room or goes to a doctor, just to focus on medical treatment, and the child is 17, the child needs parental permission and consent and when the child is 18, which could be a week later, the child is no longer a child. There has to be a bright line, we recognize that and we must affirm that, because otherwise there is a slippery slope down. However, for the purposes of finding minimal risk or as close to minimal risk as possible, determining whether

there can be minimal risk research, there is the possibility which we want to see if it actually works, and we think it could work, of looking at what the risks are in doing the proposed MCM research on adults, young adults, and extrapolating from young adults to the oldest children. And so on down the line. And that is an important protocol to minimize risk for research on children that is of no direct benefit to them and we're going to recommend that. Okay?

Number three, and this is something that has become more and more important the more we've dug into it, for these purposes. Community involvement is particularly important. Community involvement in research for the public good is especially important and it's even more important when it's research for the public good in a pre-event setting that does not stand to directly benefit the individual children who are research subjects. To put it in the negative, imagine going ahead with research for the public good that doesn't directly benefit research subjects and the public doesn't stand behind it. That would be a bad situation, to say the least. So, community involvement in every step of the way is very important. This Commission is part of that involvement and is no coincidence that we therefore had four meetings on this and we've actually asked -- actively solicited responses from any and all members of the public, and this is only one stage, but at every stage this would be important. Okay, so far, so good?

Fourth, we made a decision early on in our deliberations, and Dennis explicitly endorsed this and Tom implicitly did, if not explicitly, to look at 406 standards, which are more explicit than 407 and import 406 into 407, especially in the language and the spirit, as well as the letter of the language of research, which will generate knowledge of vital importance. That made more -- was much more specific than 407 language. And we found out from Tom, in some way, why 407 language was vaguer, there was not a lot -- there was a consensus on it, it wasn't clear what it was supposed to cover and all of that has actually played out in the way it's been used. And we could, both Tom and Dennis made pretty clear, that we could do a public service by making that language clearer and making it clear, in particular, that we think, and we've gotten a lot of support in this thinking, that 407 review should be at least as rigorous as 406 review. And I think there are obvious reasons for it, but we should state the obvious in the report. So that is number four.

Number five, it is important to emphasize that in cases of 407, the Secretary of HHS makes the decision that ultimately would make this decision and importantly, not just as a matter of form, but as a matter of substance. Again, because of the nature of the issue at hand, that it needs to be affirmed at the highest level, that this research is a matter of vital importance. And it is important in our report that we make clear, that we have been asked to provide advice on these matters, both generally and in particular with regard to AVA. And we've been asked by the Secretary to provide advice. She is not delegating her decision to us. She is asking for the particular advice of a Commission that has been constituted for a broad set of interest and expertise in bioethics. So that, if I'm not mistaken, is number five.

Number six, which is the sequel to number five, in this story. We, as a Bioethics Commission, can do the Secretary significant service and we were urged, by Dennis, in particular, to do this and a group of Commission members, before the urging, had already come together and coalesced to say "we really should do this..." And the "this," is give significant

examples of what minor risk, what we can agree, minor risk in research is with regard to children, and what -- or minimal risk, to use the language of choice, minimal risk is, and examples of what minor increment over minimal risk would be, and examples of what clear -- in each case, clear ones, ones that we can agree on, the ones we can't agree on are in gray areas. And then, examples we can agree on that would be clearly above minor increment over minimal risk. Number one, two. A, I should say, B of this point, and so I look to Christine and Nita with Dan, and B, which Dan raised publicly yesterday, not only examples, but dimensions of risk, which should be considered, and these are already in a literature. There is an expert literature out there, and what we want to highlight are the areas where, we as a Commission, can agree, and we're a diverse commission, we've read the literature -- that would be helpful. You begin with the clear cases and then the IRBs, the 407 panels can work from that. So, let me just pause there. Good? Okay.

Number seven, and there was question here and I believe strong agreement. Question from Lonnie and Nelson, and strong agreement on this. This follows from the importance of the public perception of risk in a case where you're doing research for the public good; it becomes all the more important. The recommendation, which we have not prior discussed, so I want to see whether there is Commission consensus on, is that our recommendation should be that a 407 panel should include at least several public members. And by public members, it's people who are chosen, not as advocates of a particular research or not, but who, and therefore, are not researchers who invested in research or doctors who invested in research, who could also be on this panel, but a 407 panel should include at least several public members. Do we agree on that? 'Cause we have not -- okay.

And eight, and this is my last on my list, and I'll see if Jim has any or any of you. Eight is also something we haven't discussed at all, and that is the recommendation that when pre-event research in MCM consent, the recommendation and this came out yesterday, Dennis made this recommendation, that the consent should be gotten by independent monitors, not researchers or the government. The concern behind this recommendation is that the people asking for the consent shouldn't be invested in the research going forward. And therefore, if you get independent monitors, they could be seen as having no conflict of commitment, or conflict of interest, or that I would use rigorously speaking, it would be a conflict of commitment. Do we want to make that recommendation? For this kind of research, it would not be a recommendation for all research, it would be for this and the reason I pause there, is we have not discussed this and it does -- there are people available to do this, but it does require that you find independent monitors and you not just ask the researchers to do informed consent. Christine?

DR. GRADY: Would we suggest that is for 407 research or for all pre-event research?

DR. GUTMANN: No, for -- that's a question. I mean I don't think the recommendation was specific, so the question would be: Would we recommend this for all pre-event -- this is not post-event, this would be pre-event, all pre-event research, MCM research that is not of direct benefit to children?

DR. GRADY: Even if it's minimal risk?

DR. GUTMANN: Yeah. I'm just --

DR. GRADY: Yeah.

DR. GUTMANN: That's the way the recommendation was presented, it didn't ... we could distinguish or we couldn't, I mean, it's up to us, but I left -- this is the last one because it is the one we never -- all the other ones we have considered in some form, and I think we have -- I think we should make sure we elaborate a bit more, but --

DR. WAGNER: What protection -- additional protection is afforded -- what additional protection is afforded if it is truly just a minimal risk case?

DR. GUTMANN: Let me put the case and then, as I just thought about it. So, any research that goes forward that is not a direct benefit to children is going to be suspect in some eyes and I don't mean a few eyes, but substantial number of people's eyes. There will be the need to -- we're talking about minimal risk now, because I think the independent monitors for more than minimal risk is a more obvious case. The strong case that I see for having independent monitors in minimal risk is that even when it would be stipulated as minimal risk, there will be people who challenge whether it is truly minimal risk. And having-- there would be people who challenge whether consent, even with the consent of parents and the assent of children, this should go forward, having independent monitors is a small cost and a significant benefit because the people getting the consent of the parents are not invested in having the research go forward. Anita.

DR. ALLEN: Amy, in what ways might this group differ from the IRB? Are you imagining the monitor would have direct contact with the patient?

DR. GUTMANN: Correct.

DR. ALLEN: And, are we -- are we assuming a particular model of how the process in patient enrollment and consent would proceed, such that the monitors would not, in some sense, become just part of the same system that the patient perceives is simply another broker, yes.

DR. GUTMANN: There is only so far you can go practically speaking. But practically speaking, there is a difference in having people who are not themselves invested in having the research go forward, being the people who sit down with the parents and the children, explain what the research is and ask if the parent and child are willing to give -- in the parent's case, consent and in the child's case, assent.

DR. ALLEN: I agree. I think using the word "monitor" might not be the ideal word. Because we're talking about someone who would engage the patient on issues around the research. So, it's more than just, "monitor" sounds to me like someone standing on the side.

DR. GUTMANN: Correct.

DR. ALLEN: But we mean, the patient advocate ...

DR. GUTMANN: Correct. We need a different term, correct.

DR. ALLEN: Yeah.

DR. SULMASY: Two things, one is to suggest that the appropriate paradigm for thinking about this would be our -- if our age de-escalation suggestion should prove out, that it renders the decision about whether the next step is minimal risk. It still is touchy enough, that in that sort of a condition, you would want somebody like this doing the consent and not just on the more than minimal risk. So, I would support it under that kind of research, on a vaccine trial like this. And second, we can combine this with the recommendation that Dennis also made that the person who's doing this would be an expert at obtaining developmentally specific consent. So that, developmentally appropriate consent, and not just sort of an age, sort of general age category. So, it would give a particular expertise to this person as a consentor, who would also be independent of the protocol itself.

DR. GUTMANN: Correct. Nelson.

COL. MICHAEL: I have no fundamental or intrinsic problem with that recommendation. Just am struggling in my head to think how that could be distilled to practice, because the person that is going to be obtaining informed consent needs to be as expert on the risks and benefits as some of the research team. So, e facto you've put that tag on them as a research team member, yet they are independent, I just sort of wonder if, over time, could that "monitor", if you will, have contact with the research team? I just kind of wonder if intent, which sounds noble, might just operationally begin to blur. So, again, no intrinsic objection, I'm just struggling to think how one could operationalize it and still keep that intent?

DR. GUTMANN: Nita and then Christine.

DR. FARAHANY: I agree with Nelson, although I think I might go a little bit further to say, I think I'm not necessarily comfortable, that I need to put some more thought to it. But first, I think it creates a level of bureaucracy without much of a cash-out. And, I think it may actually, potentially be worse. I like Dan's idea, which is that we need to think about developmentally appropriate consent. But, I think that the researchers who are most intimately involved with the research, both have an ethical obligation to obtain consent in a fair-minded way and the suggestion that they're unable to do so in this context, as opposed to any other context, is concerning to me. So, I think we have to think more broadly about what we think the role of researchers, in obtaining consent is generally. Why we think they couldn't do it fairly in this particular perspective, and if that would create a spill-over effect in other research areas. But, as an independent objective and an independent idea, I think one of the things I have been struggling with is: how do you obtain meaningful consent in this population? So I like the idea independently of a recommendation that focuses on developmentally appropriate consent.

DR. GUTMANN: Christine.

DR. GRADY: Yeah, I guess I'm also wondering about, especially in the minimal risk context: what it additionally adds? Because we're already in a situation where we've got IRB

review; we've got community engagement; we've got parental permission and assent of the child. In addition to have an advocate is a great idea, but whether it should be required is the question that I have in my mind. And maybe it should be a recommendation more that, in the 407 examples, it's a good idea. And in the rest, in the 404 kinds of research, it's a consideration that the IRB might want to add to their list of protections for the child, but not required or something like that. You know, I think that's one way to think about it, giving them an opportunity to think about that as an option, but not requiring them to do it.

DR. GUTMANN: Yeah. So, do we agree that it would be good idea, in 407, because of the extraordinary nature of 407 that we want to recommend it? But in the other -- it should be considered by an IRB, if the IRB feels that this is a -- there is controversy over the minimal risk, but they -- or do we want to say something about 407? -- I think, and when I think about it as not somebody who is inside the research, if I were outside this particular research protocol, and thinking on behalf of public, parents, children, I think it's as much the -- to make sure that it gives the appearance, that there is a reality to giving the appearance, of not pressuring or -- pressuring isn't even the right word, not skewing the informed consent process in one way or the other. And so, I don't think one wants an advocate as an independent person. One wants someone who isn't already invested in the research going forward. That's where I see the case. Steve.

DR. HAUSER: Yes, I agree with that, and I think one of our earlier discussions at our last meeting, that was extremely attractive, is the concept of incorporating videos into the consent process. And that may not mitigate the need for this, but I think that is a very important possible way to standardize, perhaps for different levels, of the consent process.

DR. GUTMANN: Yeah, I agree, its one way in which technology can make a significant difference. Now it's hard when you have these one-offs, but -- so where are we, 407, yes, but 404, no? Hard to see the value added?

DR. SULMASY: Again, I think the point about public perception about this is so critical. And, particularly, if we're going to make this recommendation about people who are expert in obtaining developmentally appropriate assent, those persons are not going to typically be part of the research team anyway. It wouldn't be the nurse who is going to be collecting the data later, who would also be doing consent. And, that puts great burdens on that person to learn the protocol, but people can do that. And I think that the value to me is that it really does assure everyone that no one is being pressured to obtain -- to go into this kind of research, even if it is deemed minimal risk. Again, is what we're hoping will happen with our -- you know, age deceleration kind of protocols.

DR. GUTMANN: I think we're agreed on development. We need, developmentally appropriate, consent processes and where we don't -- it's not clear to us how we're going to operationalize the -- having an independent -- somebody who is totally independent of the research process. But we do want to, I think, emphasize how important it is -- we've said this before, how important it is to make sure that consent in these cases, because they are unusual cases, is both in reality and appearance, truly impartial and the consent is clear what people are consenting to. Lonnie.

MRS. ALI: Amy, we are just talking about MCM countermeasures, right? Not just --

DR. GUTMANN: MCM countermeasures with children pre-event.

MRS. ALI: I agree with Dan. And I think, also, we need to think about, we always talk about how people who are in military feel like they are coerced, or they have to do it, because it is their superior officer asking or whoever. Children too can have that kind of feeling that, you know, I want to please my mother, I want to please my parents, I want to please the doctor, so they consent. And I think that the idea of having somebody in there, who is independent, is extremely important so that child that does not feel that way, and doesn't feel coerced. As I would say, I would say pressured, I would say almost coerced, and then the idea of public perception. 'Cause as Amy pointed out yesterday, it only takes one event to go wrong, that, to really create a public outcry when it comes to children and research. So, I think, to cover bases, and just to be extra careful and protective of the child, and to have their best interest at heart, I think the independent is correct, as Dan suggested.

DR. GUTMANN: Anita.

DR. ALLEN: I think Lonnie is absolutely right. When we get down to medical countermeasure research, on very young children, the parents themselves may be very young. And so, if you are talking about enrolling an infant or toddler whose mom is only 17 or 18 years old, you have a very complicated informed consent situation. So, in terms of developmentally appropriate, we have to think about the parents, as well as the children – actually, don't we? When talking about young children. And, we talk about developmentally appropriate, but we also want to never forget the culturally and linguistically competence, and when it comes to the kind of advocates that we're saying should be onboard, I think that goes without saying, but I think it needs to be said.

DR. GUTMANN: Nita.

DR. FARAHANY: Okay, I think the question is: are we trying to achieve true impartiality or the appearance of impartiality?

DR. GUTMANN: Both.

DR. FARAHANY: So, I think if you are a patient who has somebody who is well versed on the research, who is doing informed consent with you, while it might be nice, in theory, that that person is independent, in practice, it is the same. When you have somebody who is talking to you, how you understand truly and mentally process and understand that this person has no interest, and so, therefore, this is an impartial consent process, as opposed to somebody who's intimately familiar with the research. Maybe it makes for good PR, but doesn't seem like it makes for true -- it solves the problem of a person being neutral. Now, if the concern that we have is that a person who is vested in the research cannot act impartially to give informed consent, then I think there is bigger problem with the informed consent process in this country, not just with 407 research. And so, you know, maybe the answer is there really is that problem,

and we're trying to solve it, just in this context, but that gives me greater concern about informed consent.

DR. GUTMANN: Let me just say, because I -- I see that the practical difficulties of finding people who are expert and independent of research, I see that. But I do think, and I mean, it is the case, that there is a difference between having someone -- there is a real difference, not just appearance of a difference, but there is a real difference between having someone obtain informed consent, see if whether informed consent can be obtained, who is invested in the research going forward because that person has been involved in a team that has put forward a protocol and advocated for that protocol to go forward and they know that the protocol will only go forward if they can find people who are willing to step up to it. When that protocol is not for the direct benefit of the child or the parent involved, there is a difference between somebody who's invested in that protocol and somebody who has been brought in as an expert, developmental expert in child development, who is versed in the protocol, it could be in an institution. So, suppose this was being undertaken by a clinical operation at the University of Miami hospital, there would be people at the hospital who could be brought in as experts, who weren't themselves invested in the research protocol going forward. There is a difference. It's a difference not just in appearance, but in reality. Whether it's important enough to bring somebody in from the outside to do this, I don't know, but I do know that there is a difference. Christine?

DR. GRADY: Since I do some of those as part of my job, I believe there is, there can be a difference. But I also know that it's a -- it's a burden; It's a burden on the system in a number of different ways. And so, we want to be sure that we think it is the right thing to do in all cases. And I'm wondering if some of what we're imagining in the pre-event medical countermeasure research goes -- is too narrow? So, for example, there could be survey questions that are asked of kids as a pre-event MCM research, or there could be different flavors or different strengths of antibiotic liquids. And those seem, you know, those are important questions maybe; they're important research projects to do. They are not the same as sticking a vaccine in a child's arm. And so, maybe giving the researcher some discretion or the IRB some discretion, would allow for different types of research that we are not thinking of.

DR. GUTMANN: I think we can, because there is some range of opinion on this, I think we can recommend that the research that goes forward ought to ensure that the obtaining of informed consent is done in a way that in no way pressures parents or children or -- in no way is skewed. And some of the -- we can give some examples of how -- what we would recommend, having developmentally appropriate experts in obtaining informed consent. If at all possible, having a video. So it is just clear and it is a video that gives the facts in a way that are -- you know, that is understandable. So, we have some examples. I think we can go forward with that, that recommendation.

DR. WAGNER: I'd like to offer a modification.

DR. GUTMANN: Go ahead.

DR. WAGNER: And just for the record, and for how we might want to word this, I'd like to offer a modification. I find it troubling most of the conversation we've had about the merits of this seem to hinge on a concern that we have some suspicion about the researcher and their concern for the welfare of the subject. I am more -- when I think this is a good idea, and I'm still on the fence, I am more compelled by the notion that we should have concern for the child and the parent understanding of what is going on. So, instead of using language that says we want to make sure the child is in no way pressured, it's more compelling for me to make certain -- want to make certain, that the child is fully, and parent is fully and sensitively informed. And it may be that a third party person will be much better at that than a researcher. But I wouldn't want our conversation to be centered around suspicions that we have about over aggressive and eager researchers.

DR. GUTMANN: Dan.

DR. SULMASY: To respond to that and actually to Nita as well, this really is a problem. Usually, it's sort of a minor problem. But I've been on a data safety and monitoring board in which one of the things we saw -- and nobody was being hurt by the protocol, but there was one place where there was 100% consent. That is an ethical problem. You know 100% of people shouldn't be when somebody asked, the doctor just said, "well, my patients like me." You know, and that sort of thing happens. And, I think, usually, if it's not terribly consequential, you know, we sort of say we try our best to be independent and we push that. But in this case, I think we've got to be very sensitive about any sense there is any kind of pressure like that, even in the subtle ways investigators are not even consciously aware of. And build those sorts of protections into something as sensitive as this.

MRS. ALI: I'm with Dan. There is nothing that would keep me from protecting a child and taking it to the next level. I mean, we're talking about children here. And, as Anita pointed out, some of the parents are young, so I think that I totally agree with you, Dan.

DR. GUTMANN: So, where are we on this? Nelson?

COL. MICHAEL: I mean, I started off agnostic and I think I'm probably still there. I think these are very specialized cases, obviously. And so, I think that you could make the argument, operationally, that I shouldn't be concerned, because you could figure it out for the scattered number of cases that might occur and might not even be any. On the other hand, this is the issue where even a single concern, or impression, or implication of improper research activity would, potentially, blow up the whole enterprise and could have a ripple effect. I think I might approach it from the standpoint that, we're talking about having community engagement at level of the 407 panel. We're going to have an independent data and a safety monitoring board, that should also be done with some degree of transparency. So, I think if we're going to approach this concept, I think we do it with the idea this is not the only line of defense for these children. That there are other things that we're doing to make sure that all the community, if you will, this includes research team, have visibility and transparency, is paramount. So, I think in that framework, I think it might provide a little more latitude. Dan's idea about having someone have developmental expertise may assist with some of the concerns I'm seeing across the aisle in terms of operationalizing this, 'cause they would actually add value intrinsically to the research

team that may not have people with those skills. So, I think it probably could be done, but I would not underestimate the difficulty in operationalizing this. I think, again, it's a noble idea intrinsically, but I think really getting it done would pose operational challenges to the research team, but it could probably be done.

DR. GUTMANN: Barbara.

DR. ATKINSON: I've been struggling with this and listening to everybody and I like having it optional, except that I really am on the side, I think, for the 407 piece, having it less optional. I mean, I don't see that as very many kids. I don't see it as a huge burden --

DR. GUTMANN: I think we all agree on the 407. I think the 404 -- or at least the vast majority of us do on the 407. On 404, or 406, or whatever it is, one possibility I just throw this out, just thought of, is -- which doesn't have operational problems, it would be -- just adds a person -- is having somebody observe the informed consent process. This is -- so I -- I want there to be important research moving forward with children that benefits children and makes sure that individual children, who are research subjects, are not put under a suspicious cloud, that they are being, in any way, exploited or used. One challenge that the informed consent process was skewed, was biased, we really didn't know -- saying after the fact, has the potential -- in these cases, because they're very special cases, that's why we're here -- having somebody who, at least is part of the informed consent process observes it, could be a way of doing this -- to make sure it goes forward in an impartial way. Nita.

DR. FARAHANY: I agree with Jim, that part of my concern in the conversation is the idea that we are questioning the motives of the researchers. If that really is a problem, as you say Dan, I would recommend that that be, that informed consent generally, which is something we've heard throughout each research, via topic, that we consider taking on independently as a Commission. Nevertheless, I am supportive of optional language, framing it in the framework of saying, we think that obtaining fully informed consent is particularly important in this context. And some of the ways in which we would recommend doing so are having people observe the consent process. Having developmentally appropriate consent procedures that ensure fully informed consent, videos, etc. And so, if it is optional language that says that the thing that is not optional is obtained fully informed consent, but the mechanism by which we do so is optional, and for considerations as part of the IRB process, I would be in support of that.

DR. GUTMANN: Okay. Some of us would want stronger language, but we can -- at least that strong is fine. I don't think, just on the record, I don't think it's a matter of suspecting anybody's motives. I think it's a matter of ensuring that informed consent is truly as informed and as consensual as possible, and you don't have to suspect anybody's motives, you just have to understand that human nature, being what it is, we all trust ourselves much more than we trust others and that's an important thing to recognize. And experts trust themselves as, Danny Kahneman and other behavioral psychologists and behavioral economists have shown, experts trust themselves even more. Although, Americans tend to trust themselves a lot, as we know by surveys of American students who rate themselves very high in how they rate compared to others. But when they are actually tested on the skills that they rate themselves very high on,

don't test particularly well, so -- ok, I'm glad we spent the time on this because it was -- Yes, and we are going to move on and I think we've reached at least a reasonable consensus.

DR. WAGNER: Thanks Amy for all that. From my notes, and I chatted with you a little at breakfast about this and may not be worth adding to your list or it may just be a footnote. I thought Tom Beauchamp, in describing their Commission's work, the National Commission's work and the Children's' report, in particular, I heard him making, what I thought was an interesting point, that they, like us, spent a lot of time talking about the risk of research. Some time talking about the threat of and consequence of exposure, okay? And we were talking about, you know, the degree in which imminence is tantamount to exposure. And that there is relatively little language, and maybe there only needs to be little language, but he was urging some language, I heard him say, on the benefits of the research. And, maybe it's just for us to affirm the same sort of provision that they are reported on saying that there should be -- you know, they had talked about the three parties who must agree to the benefits of doing the research and whether or not that shouldn't be another point that we glean from their conversation inserted into our --.

DR. GUTMANN: That is good because it's implicit in our framework, and we haven't made it explicit, that there actually are three parties that are involved in affirming the importance of this research. There's an independent commission, and that's us in this case, there's the Secretary of HHS, and there's an IRB or 407 panel. And I think it's worth making that there are three separate parties and they are independent parties who are party to discussing the benefits of the research. Now, we aren't one that does the research protocol anyway, so, we have to make that clear, that we're not affirming a research protocol. But that's consistent with -- yeah, yeah. Christine.

DR. GRADY: I think given what we've discussed before, we could add a fourth party, and that's the community. Because part of what community engagement, I understand, entails is having a discussion about the benefits of doing the research and the risks of doing the research. So, they have to have some acceptance of the benefits. Can I make another point about --?

DR. GUTMANN: Yeah, and I think we could add to that, again, not to be bound -- but Tom was representing what they did, but I think we should add to that, that it is important that at least one of those bodies, and in that case it's this body, but that's just incidentally true, at least one of those bodies is open to public deliberation. And, because the Secretary of HHS can't, herself, conduct -- I mean she can go out into the community, but her time is limited and she's a singular person, but I think it is important that at least one of those bodies, if not more than one, is open to public deliberation and makes its deliberations public. Because that's another way of bringing -- when you say community involvement, there are many, many communities who are potentially involved in this and there has to be at least one of those three bodies that is, of itself, a deliberative body. And, I think that underscores our explicit endorsement of democratic deliberation for these purposes. And, you can see what a difference that makes. We didn't begin with a report. We have developed a lot of important features of this report through our deliberative process. Okay, good -- thank you, Jim. Christine.

DR. GRADY: Two comments on your list, if I may? One is the age de-escalation process, I mean, I think we have all agreed that it's a very important way to minimize risk to children, to use a process of de-escalation, but I just urge us not to be too prescriptive about what the ages are, or you know, or the fact that it may not work in every case and it depends on the studies.

DR. GUTMANN: We will, we will-- it will not be.

DR. GRADY: So, that's one comment. And the other comment is we are going to try to put ideas and examples in the categories of minimal risk, minor increase and greater than minor increase. We've already started to do that. One of our Miami colleagues gave us a document that SACHRP had worked on this same issue and tried to do that, and I think, I just want to say publicly that I think that, although, we should try and do best as we can, we should be humble about our ability to be convincing, because other people have tried to do this in the past and it seems that there is a lot of disagreement.

DR. GUTMANN: So, what I suggest, I suggested this yesterday, publicly at the meeting, and I hope we can agree on it because I think it is the only way we're going to add value here, is that we not try to be comprehensive, but we try to give clear example of things that everyone on our Commission can agree are minimal risk. And then, for minor increment, pick those things that some people will say are minimal and other people will say are minor increment over. But we also, therefore, can all agree that those are no more than minor increments. Then, and everything we can agree on goes out because we don't have a case in front of us. So, let's give clear examples that we can all agree on, that's -- and then things we can all agree are more than a minor increment over minimal risk. Those will be the guidelines we give, and we show that while we do have disagreement on -- you know, in the gray areas, that just because you can't agree on whether dusk is more like day or night, you can agree on what is day and what's night, and that's what we should do. And that's where we can be of service, and I think that to being humble in the sense we're not trying to be comprehensive, and we're taking the work of other bodies and seeing where an independent body, who isn't invested and can agree. And if we can't agree on that, then we have failed. And we should just say, we can't even agree on that. But I think we will. I think we will be able to get at least a couple of examples, maybe more, but at least a few examples in the minimal risk, a few examples in minor increment, where some people would put it minimal, but others would say minor increment. And then other examples that are more, and not trivial examples. And then, we also do what we agreed on, give dimensions of risk that should be considered because that is really important in the informed consent process. It's going to be really important to distinguish, for parents and children, what kind of risk this is. The difference between having a sore arm afterward, which poses no risk whatsoever to health beyond just the sensation of sore arm, to those things that are -- have a different dimension of risk. Dan.

DR. SULMASY: Yeah, I agree with that, I -- the way I was thinking of it was sort of anchoring the examples. Sort of, these are the clear ones and then we're going to have fuzzy things in between. And then secondly, at each of those levels that we distinguish, not only the dimension, but as we said yesterday, the sort of risks that are associate, examples of the risks

associated with the procedures that are necessary to deliver the intervention or to monitor the intervention where we sort of know those risks versus the less knowable risks that are associated with the intervention itself, which is the experimental protocol. So, that we give examples in all of those kinds of categories at each of the levels, for anchoring purposes. We can do that.

DR. GUTMANN: I think we can do that and I think we should make sure that those of us on the group and you know just Lonnie and me, for example, who are not either medical doctors or stand outside, we have the same perception as those on the Commission who are doctors and, you know, if we can, you know, agree, I mean Jim is in the non-doctor category, too. I think we can try this out on some of our friends who are not, either academics or doctors, you know, and try the examples out and see if they work. And then, I think we will have done a public service in giving clear examples that are not trying to be a comprehensive list. Because most of the other groups who have tried to do this and tried to do this for a far broader purpose than ours. I think we may do a public service, because it may turn out to have a broader purpose, but for this kind of research, which is limited, it would be good to use clear examples.

DR. WAGNER: Yes, the proof will come in that exercise, and you mentioned a word earlier I would like to, you mentioned in your list, these dimensions of risks; severity, duration and those sorts of things. I believe in the piece, Christine, I didn't get to read it, that you were speaking from, there are suggestions of what those are and we would want our illustrations, or examples to illustrate those dimensions, inform those dimensions.

DR. GUTMANN: Good. Okay. One other, I wanted to turn to Nelson and ask -- let me just give just an overview of where we are and left off. So, we talked about ethical consideration associated with pre-event, pediatric medical countermeasure research.

We concluded that, in general, such research should proceed only if it presents minimal risk to research participants and we talked about the various protections there. In rare instances when this is impossible, we talked about proposals for pre-event research proceeding to a national level review, under section 407. And, if it presents no more than minor increase over minimal risk to participants, we will give some examples of what counts in that way and we will flesh out the standards of 407 review.

We talked about the application of this approach to AVA. At previous meetings we heard from experts, that as a result of routine distribution to members of the military, AVA has been studied with young adult populations and observational studies with young adults contributed to our knowledge about safety and immunogenicity of AVA. Yet, some experts also told us that additional data from adult populations -- information, for example, from dose baring studies is needed before pediatric testing can begin and we're going to recommend that those studies go forward.

In the future, with existing information and additional data from young adults, it may be possible to design AVA research with 16 and 17 year olds that involves only minimal risk, we're open for the experts to figure out, Christine, what age categories work in de-escalation. Once these data are obtained, it similarly it may be possible to design minimal risk AVA research for

14 and 15 year olds. Again, I'm using that as place holders and subsequently younger children using the step-wise age de-escalation process.

We don't believe that 407 review, as a consequence, would be appropriate at this time because there's preparation needed for it, and I just wondered if Nelson, you want to elaborate in some ways on where you see us here?

COL. MICHAEL: Thanks Amy. So, I'll approach my comments from my own frame of reference as a physician, scientist, and vaccine researcher and engaged my entire professional life on the development of vaccines to reduce transmission of HIV/AIDS. The acquisition of HIV infections in Sub-Saharan Africa, which is the center of gravity of the pandemic, begins in early adolescence in African girls. While a single large vaccine trial has shown modest efficacy in young adults, the level of protection in that trial was not deemed sufficient enough to license that vaccine at the time. However, those vaccine types are going forward to be tested in Sub-Saharan Africa, with the hope that they could eventually become a public health intervention. So that has generated a very large-scale effort in this approach that our group and many others are part of. But it is nearly certain at this writing and I'm pretty close to the research teams, and will actually be executing part of the study ourselves in Mozambique.

It is certain that the initial studies, looking at the next test of these vaccine types there, will be done in young adults. And there was a lot of discussion with the research team about looking at the individuals that are, frankly, most at risk, which would be younger girls. But it's pretty clear at this writing, looking at normative bodies and the regulatory authorities in the countries involved in Africa, that I think that is going to be a bridge too far. So, here I emphasize that to start with because here we are not speaking in terms of uncertain risk. We have very good information with the transmission intensity of HIV is in these communities. We have a very, very good idea of what the impact of that disease is, which is becoming increasingly manageable in the developed world, but it still remains very challenging to treat in the developing world, despite the advent of multi-lateral and bilateral assistance programs.

So, our study design discussions are clearly focused, that first, we would look at at-risk adults and then, if there were efficacy signal, now I'm talking about probably 2019 to 20 year range, when we have that signal. And so it's a long time. Then, and only then, if that study was to achieve benchmarks that were predetermined a second study would be done in 11 to 17 year olds. So, turning to pre-event AVA research, the first question to ask is: what do we really know about the safety and immunogenicity of AVA in adults? And, the license pre-exposure prophylaxis, on getting pre-exposure prophylaxis regimen is a half cc given intramuscularly at 0, 1, 6, 12 and 18 months. However, the post-exposure recommendation from the 2009 CDC guidelines for post-exposure prophylaxis, under IND, would be an accelerated schedule, same dose as AVA, but this time given a different route—subcutaneously--and given more rapid sequences, 0, 2 and 4 weeks. There is no body of clinical data on the safety and immunogenicity of AVA in children. What is the optimal AVA regimen for children in terms of dose, and schedule, route administration in terms of critical research results of staging immunogenicity? What are the correlative risks of infection and mechanistic correlates of protection for AVA and animal models and, by extension, of vaccinated adults?

So, in my view, these are critical questions to ask, up front, as they would inform AVA vaccine research by refining our knowledge of the mechanism of the protective AVA induced immune response in the context of providing extended safety data with this product. Dose titration, in particular, we discussed many times, raises the potential benefit to identify a lower dose of the vaccine that could, theoretically, preserve the protective immunity response, but would potentially reduce vaccine associated adverse events. If this were to be shown, it would accrue to have logistical advantages that we discussed at previous meetings, lower doses of vaccines means you have a larger availability of vaccine in the strategic national stockpile that could be deployed. And so, you would basically stretch your vaccine. So, given our Commission's concern about endorsing greater than minimal risk in pre-event research with no current benefit to pediatric research volunteers, it seems logical to me to explore the questions that I've outlined above first in 18 to 20 year old range adults, upper range of that could drift up a bit. Especially in terms of adding expanded safety data. The assessment and levels of risk could be made in young adults with increased statistical confidence. This is something we talked about yesterday, that started in baggage claim area with Christine and I, which is, intrinsically, you can't change the levels of risk, but statistically you have a larger denominator of individuals that didn't have a severe outcome, a severe adverse event, than your numerator could be put into better statistical confidence, and that might inform subsequent studies in the age de-escalation approach. So, that is where I'd like to start.

DR. GUTMANN: I think that is an excellent summary of where we've come. And I think it's a terrific recommendation that, frankly, doesn't even have to wait for our report to come out to be acted upon. So, I think we would urge the relevant agencies to get started as soon as they feel that they can put together protocol and our public deliberations are available on all of what is needed to get a process going, right? Good. Thank you, Nelson, very, very helpful. I'm going to send this up so we can segue to the session on -- please, please.

DR. SULMASY: Just as Christine started to go back to some of your own comments, to footnote them, just with number four on the importing 406 into 407. a) I would strongly urge us not to use language like that.

DR. GUTMANN: Correct, I agree, I was using that as a short answer.

DR. SULMASY: But to emphasize that we, the way we have done so, has been through expanding the language that is already in 407, by defining what reasonable opportunities, serious problem and sound ethical principles are. That is the way in which we are, in fact, beefing those up to make it have the rigor that was in 406.

DR. GUTMANN: Thank you, that is helpful so there is no one misunderstanding. The only thing that resembles an importation is the vital importance language. The sound ethical principles we have really elaborated, based ... starting with the Belmont principles, adding democratic deliberation, which is an important part of what was implicit and is explicit in all of our studies and so, very helpful addition.

DR. SULMASY: And then take --

DR. ALLEN: On that exact point, because I also had a comment about 406, and the importation. Is there any reason to think we might need to recommend a rewriting of the regulation to reflect our --?

DR. GUTMANN: Highly impractical to hope for that. If we want everything else we're recommending to go forward, it would be good that we say, I think it is true, it doesn't require re-writing, because it's open enough that everything we're recommending could be part of case law, the way it's done. So, the recommendation could simply be that this is the way the 407 should be understood. We could -- we could recommend that it be rewritten. I just think the process that I know of rewriting these things is so laborious, that I wouldn't want to stake a lot on that, but I'm open to, you know, being persuaded otherwise.

DR. ALLEN: I don't necessarily want to persuade us to go down that route. We wouldn't be doing the rewriting, but if we think there is something fundamentally unclear or inadequate about these regulations, it couldn't hurt to just suggest, in a way, which wouldn't require additional work on our part, that there be some consideration given to a revision of the regulation.

DR. GUTMANN: So, if we were asked here, this is a really helpful point, I think, because it opens up something that we weren't asked to do. If we were asked to comment more generally on 407, I think we would say, but I'll speak for myself, I would say 407, as it is now written, is invitation for cases that should never come to 407 review to come to it, and that is what has happened, and that is unfortunate. So, in the spirit, I think, of what Anita is saying, we could signal that the recommendations we're giving for interpretation of 407, in the case of MCM, really apply more generally and it might very well, or we could say -- would be helpful to use those considerations in 407 more generally.

DR. SULMASY: And then just the second comment was on your number five, regarding the Secretary of HHS making the decision of what's of vital importance. I think that it was fruitful yesterday to hear Dennis Thompson suggesting we give some guidance to the Secretary about what sort of things go into making that decision, if we could, and we haven't discussed that, but I think that would be, his suggestion was that would be helpful, and I wonder if others agree with that?

DR. GUTMANN: I thought in earlier sessions we had talked about, maybe, I look to Lisa, talked about what we thought vital importance meant. It is the -- and I think it is important to say something in the report about what we think vital importance means. It is not within, I think, our timeframe of doing this report to, again, do a comprehensive sense, but I think what you are suggesting is that we just have some sentences about what, for example, we think of vital importance. I think that would be helpful. Yes? Good.

Okay. I'm going to summarize so we can segue to our next consideration of our next project. So, we made great progress yesterday and today in finalizing our approach, our conclusions, our recommendations on pediatric countermeasure research. We'll have to put it pen to paper, or fingers to keyboard, and put this in writing.

Critically, we concluded that, in general, pediatric research that presents no prospect of direct benefit to children or that is not likely to yield generalizable knowledge about the participant's condition, can be conducted only if it presents no more than minimal risk to participants. Pre-event pediatric medical countermeasure research which presents no prospect of direct benefit because no children are affected by the condition at issue, therefore generally can proceed -- can proceed only if it is minimal risk research. A minimal risk research design is possible if all necessary research with adults is completed. That's relevant to this research. And minimal risk can be inferred, we recommend, through a step by step series of studies from the oldest children to the youngest necessary. Only when a minimal risk research design is not possible might propose pre-event medical countermeasure research proceed to national level review under section 407.

But, and again, importantly, even under Section 407, pre-event medical countermeasure research can proceed only if it presents no more than a minor increase over minimal risk. And we are hard at work giving examples and dimensions of both the minimal and the minor increment. This means the research risk imposes a narrow expansion of minimal risk and should and, again, I quote, "pose no significant threat to the child's health or well-being," any greater risk is ethically unacceptable.

Post-event medical countermeasure research, by contrast, and imminent, and post-event would also be considered if there is an imminent threat, may present a prospect of direct benefit to participants or be likely to yield generalizable knowledge about the participants' condition. Still, studies should be minimal risk, if possible, and research protections must be in place for pediatric participants and we have discussed at length some of those protections.

We concluded that post-event research observational, post-event observation research should be planned in advance and be conducted when untested medical countermeasures are administered to children in an emergency. In addition, for post-event studies, adequate processes must be in place for informed parental permission and meaningful child assent. The research design must be scientifically sound, children enrolled in research must have access to the best available care and provisions must be made to engage communities throughout the course of the research.

We also discussed the regulatory mechanisms through which medical countermeasures would be distributed and evaluated in an emergency. So that's just a very high level review. We settled upon many important conclusions and recommendations. We're well positioned, soon, to report our conclusions to the President and Secretary Sebelius. We still have some important final drafting work to do and we should be able to do that in a matter of some number of weeks, and we will come up with an internal schedule so we can finalize this.

And with that, we should take a 15-minute break, reconvene here at 10:40. Let's reconvene at 10:40, so maybe -- I've given you an extra five minutes, there you go, thanks very much.