



**Presidential Commission**  
*for the Study of Bioethical Issues*

**TRANSCRIPT**

**Member Discussion**

Meeting 12, Session 3

January 14, 2013

Miami, Florida

DR. GUTMANN: I'm going to ask our commission members to assemble so we can get started, and welcome everybody back from lunch.

We're going to turn to the ethical considerations associated with pre-event medical countermeasure (MCM) research and such studies -- just to frame -- present no prospect of direct benefit to participants because prior to an event or an imminent event, no children will be affected by the condition that the countermeasure is designed to treat. And generally, research with children must pose no greater than minimal risk to participants.

Greater risk is only permissible when research presents the prospect of direct benefit to participants or generalizable knowledge about participants' conditions. It may also be permissible under exceptional circumstances and with national level review, a situation that we've discussed at length at previous meetings. These exceptional circumstances are contemplated at 45 CFR Section 46.407, which we have termed, and is commonly known, as Section 407 in our discussions, or we'd speak of 407 reviews.

I think we must start our analysis with a strong statement that generally pre-event pediatric medical countermeasure research cannot be done with children if it presents greater than minimal risk. Pre-event pediatric medical countermeasure testing should be conducted with the minimal risk research design. Such a research design is possible.

First, all prior testing to identify and understand and characterize the research risks, for example, modeling, testing in animals, testing in adults should be completed. Then progressive age de-escalation in the oldest children to progressively younger could begin. The idea here is that if an intervention is shown to be minimal risk in 18 year-olds, it might be possible to infer that a study with the oldest children, for example, 16 and 17 year-olds, would present only minimal risk. Then once tested with the oldest children, the next youngest group of children can be tested with an inferred minimal risk protocol.

There may be key points along the developmental scale where age is just one of the factors, depending on the medical countermeasure being tested. For example, during puberty, it might be important to separate groups into stages of puberty as well as age. Only when unusual circumstances prohibit completing such testing in consenting adults and developing a minimal risk research design can pre-event medical countermeasure research with children involving greater than minimal risk proceed under Section 407. Such research may proceed to national level review under 407 only when researchers have demonstrated that it cannot be conducted in a way that poses minimal risk to participants.

So, critically, such research can only proceed if the risk posed to participants is no more than a minor increase over minimal risk. This is the level of risk permitted under Section 406. Risk that is capped at a narrow expansion of minimal risk, and that again, and I quote, poses no significant threat to the child's health or well-being, end quote.

It is especially appropriate here given the circumstances presented by pre-event pediatric medical countermeasure research, particularly the uncertainty surrounding whether an event will occur and, thus, whether children will ever be affected by the condition at which the research is directed.

So we discussed a framework for Section 407 review at length in Chicago, and I don't think we need to repeat the details of that discussion here. In broad strokes, we discussed how to specify Section 407's criteria by first, clarifying the circumstances in which proposed research presents a reasonable opportunity to address a serious problem; second, specifying and elaborating a rigorous set of conditions necessary to determine whether the research would be conducted in accordance with sound ethical principles; and third, reiterating the importance of informed parental permission and meaningful age-appropriate child assent.

In our report, we propose to focus our discussion of this framework on its application to pre-event pediatric medical countermeasure research keeping in mind that it should only be applied in rare circumstances where it is impossible to design minimal risk research. And we can recommend that reviewers assessing a pediatric medical countermeasure research protocol adopt and employ our ethical framework to ensure the thoroughness and ethical rigor of their 407 review.

So, what I've done is just summarize our conclusions at the end of the Chicago meeting, and I wonder if members want to elaborate or otherwise comment on this summary. And I just happened to look at Christine, and she is nodding. So, Christine, I will call on you unless you tell me you don't want to be called on.

DR. GRADY: I'm happy to be called on. I'm not sure I have much to say in elaboration of what you just proposed. I think, continuing our pre-lunch conversation, it makes sense that research that can be minimal risk should be designed as such. But, research that can't, in certain exceptional circumstances, could be approved under 407 under the rubric of the framework that we've presented. And that seems right to me.

DR. GUTMANN: Yeah. We elaborated a very, I think, sensible good framework which expands what cries out for expansion: what the sound ethical principles are, which we extend from the Belmont report, what a serious risk means, and so on. I think we've gotten good response to what we've done, but I just want to give people an opportunity to comment. Nelson?

DR. MICHAEL: I'd like to amplify in some of the discussions we had. This discussion actually started at the baggage claim area in the Miami airport with Christine and I. About when you do de-escalation, you're not inherently changing a question, a real research question that is a minor increment over minimal risk to minimal risk.

However, there may be circumstances in which individual panels or IRBs could then review an increasing amount of especially safety data and come to a different conclusion downstream, which is why I think it's important to conceive of possibly doing pre-event testing with certain medical countermeasures in a deliberate way as you describe; because, especially in terms of safety information, the greater that safety data file is, the larger the denominator becomes and the numerator remains relatively low, I think you begin to change the ethical and clinical equipoise or you could potentially do that.

So I think it's an important clarification of some of our discussions we had before lunch. So, I do think there is merit to increasing, especially, the size of a data file, in individuals that would be --let's say, for sake of argument -- between 18 and 25 years of age.

DR. GUTMANN: Raju?

DR. KUCHERLAPATI: Amy, I know that we have talked about this particular aspect very

extensively, but I wonder whether that it is being too rigid; the definitions that you have articulated, and whether the circumstances might depend upon what the kinds of threats that we're thinking about. That there may be certain types of threats that may be so severe that there may not be any opportunity to be able to do anything, you know, if the event occurs. That if you don't have the information, that that might cause, you know, greater damage to the children.

And are those circumstances that we could conceive of, where this more than minimal or in a minor increment over minimal, it should be the criterion, or whether there should be circumstances where there should be some allowance by the IRBs or some other organizations to be able to allow, you know, greater than minimal risk to do the experiments.

DR. GUTMANN: Just so we're clear, 407 review is for more than minimal risk. So we are saying that in events which we -- under circumstances that we now don't have specifics of, and this is not -- this is general, there can and should be 407 review. Anita?

DR. FARAHANY: Nita.

DR. GUTMANN: Nita. Sorry.

DR. FARAHANY: It gets confusing.

DR. GUTMANN: I think that was the first time I did it.

DR. FARAHANY: It is. It is. It's impressive, you know, several years later. Right?

DR. GUTMANN: It's that one A that gets me.

DR. FARAHANY: I think one thing that I was struggling with and thinking about our post- events conversation this morning, and with Raju's comments on more than minimal risk -- you know, not making things too rigid -- is, if we can look at a post event scenario and forecast what we would expect; and let's forget the anthrax example for a minute. Let's imagine a different scenario. So, we can look in advance and say there aren't adequate countermeasures which are available in a post event scenario and we think that the likelihood is relatively high. We've talked as part of our framework before, in thinking about not just about an ethical duty to protect children, but also the ethical duty to act to ensure safety in the event of an event.

So one concern that I have, which I think we've addressed in our framework, but I just want to highlight to make sure that we do in our report as well, is that we need to balance the availability of countermeasures, the likelihood of an event occurring, and ensure that, where necessary, we don't let the structure that we've created prevent pre-event testing to develop different countermeasures to protect children in the event that something does occur. Right? So there's an ethical duty to take proactive measures to develop and test countermeasures in children to ensure that they're available in the event that something actually occurs. So --

DR. GUTMANN: So, let me just say that that's an incomplete statement. The ethical duty has to be qualified by the ethical nature of the research you would do on children who do not stand to directly benefit from the pre-event research. And that is not a balancing. It is

because the children who are being researched for no direct benefit are not on the same scale as the social benefit that might accrue in the case of an event.

And so what the 407 review does, and what our clarification of it does, is allow this to go forward for consideration by saying that there's a reasonable opportunity to address a serious problem; specifying the conditions under which it would be done, under sound ethical principles. Already we're in the realm of more than minimal risk research. And also, reiterating the importance of informed parental permission and child assent, where age appropriate.

One also might want to think about procedural, and we've talked about procedural safeguards here. That the review is done, and we should elaborate this, because it's already built into the 407 process, but we want procedural safeguards that the people who are making these decisions are not in a conflict of interest position, or of conflict of commitment position, of being pushed to unduly weigh risks one way or the other.

But, the main point I want to make is that the pre-event, there's still certain ethical safeguards that need to be placed on the risks that individual children who do not stand to benefit could be subject to.

DR. FARAHANY: I absolutely agree.

DR. GUTMANN: Good. Okay.

DR. FARAHANY: The point I'm making is not that there isn't, right? We have fleshed out well, and I agree with the framework that we've developed around ensuring that any such research is considered under a particular framework to allow it to go forward under certain circumstances. It's a slightly separate point, which is, as you develop post-event protocols, the more you learn about how difficult it may be to roll out post-event protocols or respond as quickly as would be necessary to do so in an event, that guides you to say what needs to happen pre-event is slightly different under different circumstances.

So, if you have a complete framework that looks at both pre-event and post-event and recognizes there are not adequate measures that are available in a post-event scenario, therefore, in this particular set of risks that we're considering, there is a greater ethical duty to act while acting under the ethical constraints necessary to do so. It simply adds a layer of when one should act in a pre-event situation.

DR. GUTMANN: Yeah. So that's really helpful. It does two things, actually. One is it underlines how important it is to do everything in preparation for post-event. And also, once you know everything you can do in post-event, it gives you a sense of what is or isn't ripe for 407 review. And this is -- we're talking in the general case, so I think that's helpful.

DR. WAGNER: Let me ask for clarification on that. So is it the sense then of the commission that there is certain pre-event planning and preparatory activities that not only are ethical to do, it's probably unethical not to do them. We talk about distribution plans and that sort of thing. So, we all agree to that.

But now I think I see a little more flexibility in the conversation than I thought I was sensing before lunch that with regard to pre-event research, not pre-event planning and prep, but

pre-event research. We do imagine that there could be a narrowly defined level of risk, slightly above minimal risk, that we would acknowledge as acceptable for pre-event research.

DR. GUTMANN: So let me further clarify that. Because I think what we are saying -- no, I --

DR. WAGNER: I'm asking.

DR. GUTMANN: -- is that in the event that there is a proposal of the need and the usefulness of minor increment above minimal risk in pre-event research, we are recommending it go to 407 review. And we have elaborated the sound ethical principles, which are totally unelaborated, that should guide the review.

We have clarified the circumstances of what a reasonable opportunity and a serious problem are. We've done that in our previous deliberations. But what we aren't doing -- and we really are not authorized to do -- is say whether such research would be or should be approved or not approved. In that sense what we are doing is clarifying standards which should be used, on our view, and then it will have to be a specific protocol and be reviewed under 407 review.

DR. WAGNER: And so we're allowing folks to ask the question under the right circumstances-- you know, let me just be a newspaper reporter for a moment -- that we could imagine there are right circumstances where we could ask the question whether or not it's risking injury to our children a little bit to avoid them from being injured a great deal.

DR. GUTMANN: I just wouldn't put it that way because --

DR. WAGNER: No, but a newspaper reporter would put it that way.

DR. GUTMANN: Yeah, well, it's wrongly put. Because, I mean, it's misleadingly put because we are still in the realm of no direct benefit to the research subjects; and, therefore, in the realm that any increment over minimal risk has to be extremely, carefully scrutinized. We still are in the realm -- which is what we have specified -- that no serious risk of harm or injury to the research subjects, because they will not predictably stand to benefit.

So children and children is -- you can't -- when you say doing this to children for the sake of children, they have to be the same children; otherwise, your reporter, as you were pretending to be, would be making a grossly misleading statement.

DR. KUCHERLAPATI: I think that -- excuse me, if I may. I think that Amy, there's a subtle distinction here. I guess the way that I look at it is: Either an absolute prohibition of doing experiments with children or depending upon the conditions and the nature of the threat, whether there is some flexibility for whatever the regulatory agencies or IRBs or whatever to consider what the appropriate risk is acceptable? That's the issue. I think --

DR. GUTMANN: I mean -- well --

DR. KUCHERLAPATI: Because the way it is now, I think the way it is now is there's an absolute prohibition from doing certain kinds of things.

DR. WAGNER: You need your mic on.

DR. KUCHERLAPATI: Sorry.

(inaudible)

DR. KUCHERLAPATI: The absolute prohibition from doing experimentation on children under certain circumstances, and I am saying whether it is better to have a little bit of flexibility there.

DR. GUTMANN: Dan?

DR. SULMASY: I was just going to add that one of the conditions for doing more than minimal risk research pre-event on children that we have articulated here -- but we have to make sure that it is only a condition -- is that we have reason to believe that the questions cannot be answered doing a protocol that would pose only minimal risk. And I think that that's clear. That's the reason in some ways that we've initially began to suggest the age de-escalation protocols would be to say that there might be a way in which we could determine that we could do this at a minimal risk level.

And if it is determined that we cannot, then we are leaving some room to be able to do more than minimal risk through the sort of guidelines that we've set out.

DR. WAGNER: Even if there's no prospect for direct benefit?

DR. SULMASY: Correct. Correct.

DR. GUTMANN: Well, it is that situation that the 407 review is open to consider. We are informing that review, but not making that review for any specific instance. We have no specific protocol before us. We are not authorized to deal with specific protocols, so I think we have agreement on the framework, but we do not know how the framework would operate to a conclusion in any particular case which we do not have before us. Yeah. Good.

Are there other questions, comments, including any -- I should say, for those of you who have joined us, if you have any questions or comments, would staff please raise their hands? We have cards we could just pass them up, and read them. Are there other questions and comments on this?

Because I will -- yes. We will break when we're done with this and then come back. Steven. Steve.

DR. HAUSER: Just to follow up on this point, which I think is so important. Barbara and Dan spoke this morning about perhaps putting additional examples on what that slight increase over minimal risk would look like based on precedent and knowing what 407 has looked at in the past. And on some of the ideas that we spoke about this morning, as well as in general, the sorts of risks that we think are above the ceiling, so that at least we can get a range.

DR. GUTMANN: Right. And we've talked about that before, but that's something that we really have to put to paper and make sure we get right.

By the way, I think it's important that the body of evidence -- as far as what's been considered -- is pretty far-ranging, and so, we're going to have to come to examples that we feel

as a group comfortable. 406 reviews are more prevalent than -- as you know, there have' been fewer than twenty 407 reviews, and no more than half of those have been approved. So 406 reviews where there is a minor increment over minimal risk are much more prevalent. The body there of evidence about what minor risk is and what a minor increment is greater, and I think that would be better for us to use as a set of data points.

Yes, Christine.

DR. GRADY: Although I think there's also -- it's worth recognizing that there's also evidence that there's lots of disagreement among people and among IRBs about what is minimal risk and what is minor increment over minimal risk, so even the same procedures seen by two different groups may not be judged in the same way. The same risk, I mean. Sorry.

DR. GUTMANN: Yeah. And we will have to use examples where we think are clear, and as we like to say, you've got to define day and night and there's still dusk and dawn that people can disagree as to whether it should be considered day or night. But we will put our day and night examples out there and let the 407 process and people dig in when there's specific examples, and have to justify -- I mean, that's where the deliberative process is important. And we can't engage in a deliberative process over specifics that we don't have.

Lonnie. Oh, I'm sorry, Nita -- Anita was first.

DR. ALLEN: Just a couple of thoughts; one of them is that I hear from Raju maybe a little bit of frustration about the kind of resistant or -- I won't say anti-research -- but a kind of avoiding a resistant tone to our deliberations about this in contrast to our discussions about *Privacy & Progress*, and we're all enthusiastic about research. We're pro research. Let's make research possible. Here we seem very reluctant to be enthusiastic about the research, because it involves a vulnerable population.

And, I just think there's -- it's probably no way around that. We probably can't reach a point where we're going "rah rah research" because here the research is needed for a very grave reason and the population we'd be doing the research on is very vulnerable. I think that makes it hard for us to be the kind of very enthusiastic pro-research group that I think maybe he would like to hear us being a little bit more of.

And then one final point. I like the age de-escalation sort of solution to the problem of what kind of research can we tolerate, but I just want to make a parallel that may be a little bit scary.

But during the civil rights era, Georgia school administrators who were trying to resist desegregation, proposed an age de-escalation approach to that. Let's start with the 12th grade, then we'll go the next through the 11<sup>th</sup> grade, then we'll take it 12 years later and sometime in the 70s we'll have integration.

And I sometimes do wonder whether or not our age de-escalation process or recommendation might look to some people like a kind of a cop-out, some kind of cop-out. But I think it's not. I think there's a difference between trying to protect children from research and trying to protect children from integration.

DR. GUTMANN: I think we can all agree with that and that's where you can use very misleading analogies which you've just shown why it's not -- and -- it is the case that people who want to go full steam ahead with this research will not like the cautionary principles that we have. They're not barriers to ethical research, they facilitate ethical research.

And I would just say one instance of grossly unethical research on children would be enough to stop ethical research on children going forward in this country. There would be such a reaction among people who are not members of dug-in groups that it would be one of the worst things that could happen in this country for the cause of doing ethical research on children. And we were not asked as a Bioethics Commission for nothing to deliberate on this so.

Thank you, Anita, for that. Lonnie.

MS. ALI: I just want to ask a question. And maybe Dave knows now that he's in residence at The University of Pennsylvania. The reading that we had in our binder here, that Zeke had proposed the SERR framework for evaluating risk, and there was another article that sort of debunked it, but is that getting any kind of traction?

DR. GUTMANN: Yeah—um-- Christine? I don't know the answer.

MS. ALI: I mean when you talk about risk, minimal risk and minor increment over minimal risk, you're left up to the IRBs to their discretion, which could vary.

DR. GUTMANN: Yeah.

MS. ALI: And so if there was a structured framework, is that --

DR. GUTMANN: Great question.

DR. GRADY: That is the reason that Dave and Zeke and others put it together. Their goal was to say that we need a system of looking at data that makes the process of determining whether or not this particular procedure or this particular intervention is minimal risk or greater than minimal risk, is based on more objective standard than what we currently use. And so Dave proposed the SERR.

At this stage, it's mostly in the proposal stage. There's been a number of papers that have been written about it. There have been a lot of people who have talked about it. But, the next step is for it to be tested empirically to see if IRBs can, in fact, use it in a way that helps them make interpretations of data. So, that's where it is.

DR. GUTMANN: I would just say that there is and can be no purely objective way of drawing a line here. The line is inherently an ethical line. There are arguments that can be given for doing a line one way or another. What there can be are ways of empirically judging levels of risk and nature of risk, but where one draws the line is an inherently ethical determination.

DR. ALLEN: And individual, too. In a way.

DR. GUTMANN: Well, yeah, in a --

DR. ALLEN: I'm talking about IRBs it's the individual interpretation of risk. And I think that's what he was trying to get away from.

DR. GUTMANN: Right. So one of the things that's being attempted in that paper, and it's still in the discussion phase, is to minimize the variation among IRBs by coming to some agreement as to what fits into what category.

DR. ALLEN: Right.

DR. GUTMANN: Christine, you had something?

DR. GRADY: One more thing about this then I wanted to respond to Anita. Part of the – certainly there's an ethical decision about where the line should be and how much risk should be allowed in any case; but there is room for certainly more data and more objectivity about whether a -- you know, sore arm should be thought of as minimal risk or greater than minimal risk. And people should be able to agree more or less about that. And that's part of what the reason that this proposal was made.

I wanted to respond to your observation that we are more resistant in this case to research than we were in the genome project. And I think it's actually interesting to me. I think that the reason we are is because it's MCM research. I don't think anybody around this table is saying that research in children, in general, is not a good thing if it finds ways to treat children who are ill, or prevent illness in children.

The issue here, of course, as we've talked about already this morning, is that these are conditions that may never happen, that we hope never will happen; and so we're sort of balancing a different kind of need than we would be if it was studying a treatment for a disease that kids have.

DR. GUTMANN: On children who stand to directly benefit from it.

DR. GRADY: Sometimes they don't even. I mean, I think there are cases of research -- and that's why 407 as a category is so important to have, in my view -- there are cases of serious important research that's done for children who are ill that does not provide direct benefit to them.

DR. GUTMANN: Uh-huh.

DR. GRADY: And, so then you have to make a decision whether it fits into the 406 or 407 category and whether it's acceptable, based on the level of risk but still –

DR. GUTMANN: It should be -- I mean, I just say that 407 category has been fully fleshed out from 2000. It's been in existence for a long time, decades, but just take from -- it's been fully fleshed out from 2002 and all the time it's been in existence, there are approximately 9 to 10 approved cases.

DR. GRADY: Yes.

DR. GUTMANN: And so -- and their categories -- they're pretty hard to systematize.

DR. GRADY: They are.

DR. GUTMANN: Three other bodies, two or three, I believe it's three other bodies, have recommended to the government a systematic study of 407 cases and a categorization of them and the government has yet to do that. That's a serious problem with -- and so, we can underscore -- we've talked about this earlier, but we could underscore the importance. If 407 is the category -- now I'm totally agreeing with you that MCM has a different set of challenges. But in non-MCM research, which we were not asked to speak about in our report, there are fewer -- 10 or fewer, 407 cases. The government has been asked by independent commissions, including the IOM, to require there to be a thorough study of those, and analyze them, and that hasn't happened yet. Barbara.

DR. ATKINSON: I just want to agree with Raju on the research piece, and be sure that we do balance it out on the side of the advantages of research, too. And I would say it's like our synthetic biology where, you know, there was an unknown risk of what happens if these organisms got loose; and yet we decided that there was a greater good. And I think we just have to be careful in this balance here that we aren't completely on the other side, as Anita said and as Raju has been pointing out, that we have to show that there could be the potential for great value as well.

DR. GUTMANN: Yeah. Yeah. I don't think we are on the -- yeah. Raju?

DR. KUCHERLAPATI: Thank you, Anita, for making the comments. I think that -- I want to say, it is not a question of whether this group or individuals within this group are pro or anti-research, or is it not a question like the commission used the word "let research rip".

(Laughter)

That is not the point. I think that the goal for all of us is the same. We would like to find mechanisms by which we would be able to have the least amount of harm that could come to children if this attack were to come about. And we're discussing what are the things that we need to do to be able to get there.

And I think some of us are arguing that to be able to provide the maximal benefit for children, in the case of an event, that you might have to do certain type of research that does not immediately benefit them, and that would be considered to be more than minimal risk. And, I wouldn't be constrained or handcuffed by 406 or 407 or whatever the case may be. I think that this commission would have to stand up and say this is what we believe in.

DR. GUTMANN: Well, we should say what we believe in, and I don't believe that being unhandcuffed by all regulations is a recipe for doing ethical research on children.

DR. KUCHERLAPATI: No, Amy, but you're -- you're painting it black and white. It's not black and white.

DR. GUTMANN: I'm not painting it in black and white, and I barely said a sentence, and you said I was. But you said, and I wrote, what we need to consider what the things we need to do to get there, in order to protect children. Some of the things to protect children in the case of an event cannot ethically be done today. Just as, we looked at Guatemala, I mean, assume that

Guatemala had scientifically sound research, which it didn't, but assume that it did. And it was scientifically sound, and it was injecting pathogens into vulnerable subjects because the only way you could find out whether STDs could be prophylactically prevented is to inject syphilis, gonorrhea, and other things into patients. You can't find that out otherwise. It is ethically impossible to do that.

So I think it is important, and that's why we're a bioethics commission, to say that there are some things you could scientifically need to do to have full protection that are ethically impossible to do. We want as a commission to do everything that is ethically possible to do to protect children. And I think we can all agree on that.

We're going to take a break and reconvene at 2:15. Okay? Thank you.

(Break.)