



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

**TRANSCRIPT**

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DR. WAGNER: Let's all gather.

Okay, I believe all who are available here are assembled, and Dr. Beauchamp will join us by video conference. Tom, can you see and hear us?

DR. BEAUCHAMP: Yes, I can see and hear you.

DR. WAGNER: Much better. I was going to say you can hear us better than we can hear you, but they just took care of that here. So we have two panelists speaking with us in this session, on philosophic grounding of the ethical approach we have been applying. We'll devote - - we'll hear first, rather, from Tom Beauchamp -- and, again, we thank you for being here -- he is professor of philosophy and senior research scholar at the Kennedy Institute of Ethics at Georgetown University, and among his many contributions to the bioethics literature, he has coauthored the seminal work *Principles of Biomedical Ethics* -- published that along with James Childress and as a staff member for the National Commission of Detection of Human Subjects of Biomedical and Behavioral Research, he has also penned the bulk of the *Belmont Report*, which we've been referring to Dr. Beauchamp quite liberally.

He has received a number of awards, including a Lifetime Achievement Award for Excellence in Research Ethics from the Public Responsibility in Medicine and Research. Also the Henry Beecher Award from the Hastings Center, and the Lifetime Achievement Award from the American Society of Bioethics and Humanities. Dr. Beauchamp, we thank you for joining us today and the floor is yours.

DR. BEAUCHAMP: Thank you very much. This panel is entitled philosophical grounding of the ethical approach -- at least that's what I was told -- and my assignment in particular is to discuss, quoting the assignment given to me -- how the Belmont principles apply in assessing whether research with individual children is ethically permissible, so I'll try to not stray very far from this remit. The National Commission published the Belmont report only after it had published 16 other volumes specific to various problems of vulnerable populations. Belmont needs to be interpreted in light of these more specific recommendations in those volumes.

The children's report, in particular, would be, I believe, relevant to what you're discussing at the present time, insofar as I understand it, which would be minimal, but I'll try to keep up with you.

The Belmont report itself was not codified as the children's report was, and it really represents the model framework that the Commission thought should be before us as we deliberate about research problems.

The philosophical grounding for the Commission is the set of three Belmont principles. The Commission did not hold that its general or principles did not apply without specification directly to cases such as the anthrax vaccine case. The Commission explicitly denied that principles entailed conclusions in complex cases.

Belmont looked to educational institutions, professional associations, government agencies, institutional review boards, and presidential commissions such as yours, to provide the more specific rules and judgments that are required in research ethics. The Commission's

approach to cases and policies was first to understand the moral and policy problems, the history leading up to those problems, the nature and extent of envisioned research, the purposes for which the research was conducted, and the reasons that have been offered in support and in opposition to the research.

Is there a question? No, no, okay.

The Commission would only then debate the myriad of the options. Along the path of its deliberation, the Belmont principles were to serve as non-absolute constraints. For example, the imperative to obtain the consent of subjects, the permission of parents, and the assent of children was considered a powerful, though not an absolute constraint, on the morally-acceptable options that might be proposed. To say that a Belmont principle was a powerful constraint is to say that it's obligatory to act precisely as the principle demand unless the action conflicts with an equal or stronger obligation.

Principles served as the chief moral constraining force on intuitions and consequentialist reasoning many, many times in the Commission's deliberation. Similarly, the imperative to not exceed minimal risk in research involving children and exceptions that allow minor increment above minimal serves as a threshold limit to risk that may be used, though I will later speak about one exception -- an important exception to this general conclusion.

The Commission's report on children, I hope is pertinent for your anthrax research protocol discussion. The orientation of this report was how to protect vulnerable children by establishing conditions that research must satisfy in order to be justified, that was the focus in the overall report.

At the same time the Commission was deliberating about its conclusions, research involving children was also undergoing investigation in the scholarly literature. An extremely strong version of the principle of respect for persons and informed consent was being proposed by Paul Ramsey, an absolutist prohibitionist position that children being non-consenting, could never be used as research subjects.

This view was rejected by the Commission because it blocked too much valuable pediatric research. Another much discussed but rejected option was the utilitarian one of public beneficence, a view that children, like adults, can legitimately be used, and in some cases, perhaps, morally must be used as research subjects whenever public benefits outweigh risks to subjects. This view was rejected by the Commission on grounds that it is too utilitarian and needs to be curbed by the Belmont principles.

So Belmont rejected both absolutist theories and an absolutist interpretation of its principles.

It substituted a balancing of the principles account, and that cuts across all of its reports.

After endless debate, the Commission established five unsurprising, necessary conditions, not to say sufficient conditions, but necessary conditions, that research must satisfy in order to be justified in the use of children. These conditions are:

Research is scientifically sound and significant; if possible, animal and adult studies have preceded, as have studies with older children; risks are minimized; privacy and confidentiality are protected; and subjects are selected in an equitable manner.

In addition, and now to draw closer to, I believe, the kind of thing that you're deliberating about, research that does not hold out the prospect of benefit to subjects, and is at or below minimal risk, is justified if the assent of the child and the permission of the parents or guardians are required.

Further, and I suspect even closer to the kind of thing you're investigating, research that does not hold out the prospect of benefit to subjects, and is above minimal risk, in that case, the increased risk must be -- and here comes a long string of provisions, and perhaps I should repeat them, but I'll go over them quickly -- the increased risk must be no more than a minor increase over minimal risk of well-known conditions; interventions are reasonably commensurate with those the child was already familiar; the anticipated knowledge is of vital importance for understanding or amelioration of the subject's specific disorder or condition -- a very important one there -- and the assent of the child, if competent to do so, and permission of the parents, are also required.

So, in this case where you have non-beneficial research for the subject, and its more than minimal risk -- it can't be more than a minor increase, it has to be reasonably commensurate with a familiar situation -- the subject's condition or disorder must be the focus of the research and the assent of the child and the permission of the parent or guardian are required.

Let me now try to bring this discussion to bear on your anthrax vaccine problem, although I caution you again that I know very little about this problem, certainly nothing like you do. If this research does not hold out the prospect of benefit to subjects, but is at or below minimal risk, and there's reasonably mature assent and parental permission, then I would think it would be justified. There's been nothing in the Commission's report to say that there wasn't.

Of course, big questions here arise about the level of risk, about dosage, about efficacy and so on. And the anthrax vaccine -- in the anthrax vaccine case, and probably, I suspect, in this case, those conditions would not be satisfied. So, I would think it's probably unlikely that the minimal-risk provision would kick in and would work.

So, then, go to the next level. Suppose this vaccine research does not hold out the prospect of benefit to subjects and involves only a minor increase over a minimal risk, then it would again, presumably, be more difficult to justify, probably, I think, not justified for reasons we just looked at.

The Commission took an increase beyond minimal risk to be a serious red flag for justification, though it is not an absolute barrier. This matter was endlessly debated in the Commission, two commissioners ultimately dissented from the report because they could not accept it, and I suspect the Commission would have found this form of justification to fail in the case of the protocol provision before you, for reasons of three conditions that are set out by the Commission. In particular, the condition that there be a specific disorder or condition that the subjects already have; the condition that an intervention be reasonably commensurate with the medical and social situations ordinarily experienced by subjects; and third, there is a promise of

significant future benefits for children suffering from this specific disorder. Assuming those conditions could not be satisfied in the case, then it would not be justified.

Now, finally -- and this will be a somewhat abrupt transition -- I want to go to a part of the children's report that I think has never received very much attention. For all I know, you've been over it a hundred times, I really have no idea what you've been over here, but it is a provision called Recommendation 6 in the Commission's report on research involving children.

And it offers, still, another possibility of a hope for justification. In this provision, you have a provision that's roughly like the anthrax vaccine case. Here, the Commission envisions more extraordinary circumstances and says that non-beneficial, above minimal risk research, may be justified, if and only if, three conditions are satisfied, and that's three conditions in addition to the five that I gave you at the beginning, which pretty much everybody accepts as staple conditions, so these are three conditions for these more or less emergency-type cases.

First, it requires that three parties have found, that they have made a judgment, that the research presents a vital opportunity to understand, prevent or alleviate a serious problem affecting -- that is to say, pertaining to -- the health or welfare of children.

One, an IRB has so found; secondly, a national ethical advisory board -- that would be you in this case -- have so found, and the Secretary of the responsible federal agency have so found -- that would be Secretary Sebelius, I take it. Second condition, the conduct of the research would not violate any of the Belmont principles with respect to research, beneficence and justice; and final provision, the assent of the child and permission of the parents or guardians have been received.

Under this seemingly less stringent, though organizationally complicated set of conditions of justification, might the anthrax vaccine research be justified.

In certain respects, you are clearly much more position than I am to answer this question because only you would know if you, as a national ethical advisory board, might have made the requisite determination.

You'd probably be closest to whether Secretary Sebelius might approve it, and -- but let's suppose for purposes of this discussion that you would and she would, and therefore that these conditions have been satisfied.

The other condition of IRB certification is not one we can assess, so we set it aside, but let's assume that that threshold test has been passed, as well.

The second condition, is that no Belmont principle be violated.

The way the Commission analyzes these principles, both respect for persons and beneficence, clearly raises skeptical doubts about the use of children. Respect for persons specifically demands that we protect those with diminished autonomy.

There also may be a problem about selection of subjects. That is to say, fair inclusion and exclusion criteria. There may be a violation of equal consideration of interests, for example.

The demands of these three principles, that each have to be very carefully assessed through extensive deliberation. There's no shortcutting that process, in my view. Nonetheless, justification of the research still may be possible, and here's the way in which I would think about it, in accordance with these provisions in the Commission's children's report.

First, research is not merely a burden placed on subjects. It can also be viewed as an opportunity by both subjects and parents, and it could be so viewed in the instant case.

Second, the Belmont principle gives subjects rights, and one right they give is the right to volunteer. Indeed, children are given the right to volunteer, assuming they have a capacity for voluntary action.

The principal respect for persons specifically requires that we not obstruct the decisions and actions taken by potential subjects.

We're also required to look at whether an individual does or does not have the requisite level of autonomy. The class of children is not prohibited from this consideration.

The commission notes that whether to allow some vulnerable subjects to volunteer, or rather to protect them, often presents a dilemma. That's a direct quote. That's from the Belmont report, not from the children's report.

It does not bar use of mature children. Sparing you a tedious analysis of the principle of beneficence, it, too, is not clearly violated, and so does not invalidate the research. The commission not only allows for, but promotes consideration of long-term benefits.

I quote again, even when individual research subjects are not the direct beneficiaries, closed quote.

In its final wording, in its comment on this form of justification in extraordinary situations, the Commission is clear that in the case of what it calls a grave problem of health -- for example, a public health emergency -- where there exists a scientifically-sound hypothesis of expected benefit, where appropriate conditions for the assent of children and the permission of their parents have been secured, and the other condition -- threshold conditions have been satisfied -- then the research can be justified.

So, if those conditions have all been satisfied in the anthrax case, then conduct of the research could be justified.

I'll now conclude. In this talk, I've been representing the National Commission to you and have been loyal to its framework of justification. I haven't resolved any of the primary issues that I imagine are before you. I have, though, maintained that the only likely justification of the anthrax vaccine case, using Belmont, could come from the Commission's Recommendation 6, which merely leaves the door open to justification.

To get further than I have gotten, one would have to address each of the conditions of this recommendation, as well as each principle in the Belmont report, through a debate of the sort that I have described earlier.

But in conclusion, let's assume that ideal circumstances for justification are present in this case. Risks involve no more than a minor increase above minimal risk -- a ready pool of mature minors wishes to sign on as volunteers, proper authorities have correctly found a serious health problem needed to be addressed, and no Belmont principle is violated. Then I would think it would be reasonable to say that the research could be justified.

Now, good luck in deciding whether all of these conditions are indeed satisfied and, of course, in deciding whether the Commission's framework of justification is itself justified. Thank you very much.

DR. WAGNER: Thank you so much. Thank you, and we appreciate your wise advice, and also your wish for good luck. We need both of those.

What we're going to do, Dr. Beauchamp, is hear from our other panelist first before we open up for conversation, so I hope you'll stay with us.

DR. BEAUCHAMP: Yes.

DR. WAGNER: Great. Our next -- Dennis, why don't you join us. Dennis Thompson. Dr. Dennis Thompson is our second panelist.

DR. BEAUCHAMP: Hi, Dennis.

DR. WAGNER: We'll get your microphone on in a second. Let me introduce you formally. Dr. Thompson is the Alfred North Whitehead professor of political philosophy at Harvard, founding director out of the University-wide Edmond J. Safra Center for Ethics. He has served as consultant in the Institute of Medicine of the National Academies, to the American Medical Association, the Food and Drug Administration, the U.S. Senate Ethics Committee, and a South African parliament, among other institutions.

Dr. Thompson has also been prolific, written a number of books, including *Restoring Responsibility, Ethics in Government, Business and Healthcare*. Dennis, we're pleased to have you with us, and we turn the floor over to you. If you'll push your button on your microphone so everything gets piped through.

DR. THOMPSON: Thank you, Jim and Amy, and the Commission for inviting me. You've made considerable progress on a very challenging set of problems, which makes my task easier. I think I'm the last person to testify before you reach your conclusions.

It makes -- instead of telling you what the right answers are, I can just criticize what I think are your answers.

DR. WAGNER: Are you ready for questions at this point?

DR. THOMPSON: Yeah. If I lose my voice, it's not because I've lost my thoughts, but I think I'm an unwitting subject of some Commission experiment without my consent. In any case, I'm going to concentrate my comments on what I take to be the framework that you are poised to recommend, to use the phrase.

I'm getting my ideas about what you think -- that's what I'll be telling you what you think -- from looking at the transcripts and some of the previous meetings and listening to Amy's summary at the beginning of this session today. At least I hope this is close to what you're poised to recommend, because on the whole, I think it's sound and actually represents an important advance over a lot of work that's been done, not on this specific problem, but in this general area in past.

I'll divide my remarks into three parts: What I think you get right, what you get right but need to say more about, and what you neglect. The good, the unfinished, and the neglected. It's not the good, the bad and the ugly.

The good, first the good, and I can be brief about that not because there's

(Laughter)

--- no, no. Not because there's so little that's good. On the contrary, because anything I think I could add at this point would be not all that helpful. But just let me just list some of the things that have impressed me favorably.

The requirement -- and some of these weren't talked about today, but they've been part of your discussion, the requirement that participants in any experiment be compensated for injury.

The public may be surprised that that's actually not been part of legislation or even recommendations, and I think you would do a service by emphasizing that.

The proposal for what you're calling de-escalation research design, what the NBSB called sequential research, is I think sound and good.

The NBSB actually first proposed it before you, but the trouble with what they -- first of all, it didn't have an ethical basis in their report, and it seems a little unlimited. Once they start down their escalation, it really is -- there don't seem to be any limits.

Another point, the recognition that the risks of government-sponsored experiments -- the risks that that sort of experiment imposes, even with parental consent, are not the same -- not on the same status, ethically, as the risks to which children -- to which parents expose their children in daily life.

And then something that just came up very briefly today, Nita I think mentioned it, but it's been an important part -- and I would hope it would continue to be an important part of your report -- is the community involvement and accountability.

Okay, and there's more, but that's enough praise.

The unfinished. So, important points that I believe are you're going in the right direction, but need more thought and discussion, and I was encouraged this morning to hear you say to have more thought and discussion, but it seemed that you wanted -- you've recognized the need for this.

So, let me start with a very general point, and what I think some people who have not been involved directly with this will see as the most striking implication of the framework, is the strengthening, or at least, clarifying the standards of risk and seriousness.

In effect, what it looks like to some people, and I think it's to some extent true, you're importing 406 standards into 407.

In fact, somebody might say that this is a merger of the two, and that 407 -- the two provisions, sections, have become identical.

I think that there's some truth in that perception, and you want to be careful, more than I have heard, about making a distinction between the two. There are still differences between the sections, the most important being, I think, that the Secretary, not an IRB, makes the decision. That's not just procedurally important, but that elevates this to a national level and relates to something I'm going to say a little bit later about the composition of the panel, the 407 panel.

But the two key standards are -- now, I'm very close, so in my view, you're right to want to strengthen both of those standards, the seriousness and the risk standard.

Take them one at a time. The 406 standard for assessing the importance of research is actually stronger now in the legislation than the 407 standard.

Reasonable opportunity to address serious problems, that's 406, is -- that's 407 -- is weaker than likely to generate generalizable knowledge, which is of vital importance. The risk is higher, which seems the threshold for importance of the research should be higher.

This is an oddity in the regulations. I think I'm not the first to point it out, I think the IOM report mentioned it in passing, but you should not leave that unremarked.

And what you're doing, as I understand it, is actually bringing 406 into 407, and thereby strengthening the standard and making -- getting rid of this oddity. Nobody doubts, I think, that it's of vital importance to prevent the consequences of a deadly pathogen. The challenge is, as your discussion, once again, this morning made clear, is the likelihood of the exposure.

I know even in Chicago you spent a lot of time on this question, and it seemed as if you were then deciding to leave this up to the Secretary ultimately and some of the 407 panels.

But, I agree that there is no reasonable way to assign probabilities and that any decision is going to depend on the specifics of the -- what you can't know in advance, and even people who know them may not be able to tell you, but I think you could -- you could give more guidance to the Secretary and the panel by listing considerations that should count and some that should not.

Some examples, this will be a recurring theme -- I think several of you seem to agree with me. Maybe it's an odd thing for a philosopher to say, but I think -- and Tom also was hinting at this sort of thing -- in this area, the principles don't give you conclusions in that, even if you have all the information, there's still a need for cases and examples and exemplars and paradigms. I think that's what's going to drive the decision making.

And you can help in that by providing some of those, I think.

The other standard you import is even harder, though I agree it should be necessary. Minor increase over minimal risk, as it resonates all over here. I have always found this phrase confusing. It's synonyms piled on synonyms -- or synonyms on stilts, let's say.

For now, I will work with it, as you are. We're not in the business of changing the regulations. Let's just consider the practical problem.

The assessment of risk, whether it's minimal or minor increase, is not entirely an empirical objective matter. Which standards we use, how much weight to put on each, requires a value judgment.

And, unfortunately, and here I refer to the work of Paul Slovic and some other decision researchers, public perceptions about risk differ widely from the perceptions or estimates by experts, and Slovic actually argues and shows in some cases convincingly, that public perceptions are not entirely wrong and they represent a different way of looking at the actual risks.

So -- and as you know, and it's already been mentioned this morning, even experts disagree among themselves, and often we know from Kahneman literature, the experts are not subject to biases.

In the one 407 case that's most directly relevant to your assignment, the Dryvax trial, the reviewers' judgment about risk and even about the value of the experiment were quite divergent, actually. And this morning, several people have referred to that. And if you look at -- as I'm sure you have -- some of the other 407 cases, you'll find there's been a general loosening of what counts as minor increase over minimal standard. It's a little bit troubling. Things -- overnight hospital stays, special carb diets, Tanner staging, even gene transfer, in the case of an IRB. Some of these are IRB.

But some of them would go further than I think you should, and from my understanding of your deliberations, would, go as examples of minor increase over minimal risk.

So, don't just leave it up to the past precedent. I'll come back to that. The IOM threw up their hands, sort of collectively, left the determination to the Secretary and the panelists. I think you can, and to some extent you already have, given the Secretary more guidance.

I would expand -- this goes back to my theme about examples -- I'd expand the list of examples, giving, not only paradigms of what's permitted, but also what Dan said this morning, some examples of what's not.

Now, you know, there's always -- you're not going to be absolute. Tom made a point about that, but if you don't give some examples that people, not only the public, but experts can hold onto, you're not giving the Secretary enough advice.

I don't want to suggest that estimates of risk are purely subjective. Just because something isn't empirical doesn't mean that it's not something where there are right and wrong answers. There are good and bad reasons for estimating the value of various risks, but it does mean that it would be very important that 407 panels include public members who would deliberate about the estimates, more than one public member, not necessarily an advocate for

children, as there's an HHS advisory committee that said "we should have one public member and she should be an advocate for children". I've been on IOM and other bodies where there is a public advocate, and the poor person gets stuck with always, I'm for the children, or I'm for the public. We all are for the children and we all are for the public, nobody should have that role. But you do need independent people on -- not just experts -- on these 407 panels, and I think you need to say more about the composition and role of the 407 panels.

Okay, the neglected.

Generally, your deliberations have been admirably comprehensive, I think. There are a few additions I'd suggest. Minor increase over my minimal criticisms.

(Laughter)

Yes.

I would like, as I just said, I'd like to see more discussion of the composition and role of the panels. I would like to see stronger protections for securing assent and consent. Instead of age—you have opportunity here. You don't have to do age-related rules. You could ask the process be tailored to the specific individual children. Some 7-year-olds are more mature than others. My 7-year-old sons were not. My 7-year-old granddaughter is better.

This is not possible in large-scale studies, which we're talking -- if this happens, we're talking much smaller number of people. And to avoid biasing the process, the consent should be secured by an independent monitor, not by the government, not by the researchers.

So independent assessment, another theme running through my reactions.

Okay. Finally, one suggestion -- a very general one that applies to lots of different parts of the report and deliberations -- on many of the issues that you cover, you, understandably, rightly leave open an indeterminate -- the basis for decision. You do this for good reason, but as a result, the judgments are delegated to others who may indeed have more information than you do, but they also face more pressure, have less time, and have more bias or different biases than you.

So, I want to suggest that part of your advice to these delegated decision-makers take the form of warning against sort of cautionary notes, or what I call ethical heuristics, or biases, with apologies to Kahneman. They're less well known than the cognitive heuristics and biases, although they overlap with them. These two can lead decision makers astray even -- or especially experts. I call them ethical heuristics because they result from well-motivated dispositions to produce better consequences, even though they can actually be counterproductive.

So if you take note of these tendencies, perhaps, you know, not a list somewhere in the report, but as you go through talking about risks and benefits, you could perform a useful service in helping the decision-makers, the panels, the public, the potential subjects, to reach their decisions without succumbing to these predictable, though often unrecognized, especially under pressure, biases.

Let me just give you three examples and then my time is over, except it says I have 15 minutes, but something called benefit inflation. So, it seems like respecting persons would require you to find some benefits they would rationally accept, but there's a tendency to overestimate benefits by sort of stretching the goods the subjects receive.

Opportunity to contribute to a valuable project. or more commonly, including therapeutic benefits that come just from being in the study. You get free health care, you get attention.

Well, that's -- that's not -- I mean, that's a benefit, but it's not what should be considered in deciding whether this falls under the direct benefit provisions of 405 or -- sort of -- but there's a real -- there's a tendency to want to do that, and for good ethical reasons, but also you should resist it, or another, I call familiar analogy bias.

It seems fair to compare research risks to those that are faced by normal people in everyday life, but that leads to underestimating risks, and a failure to appreciate something I mentioned before, it's the difference between risks imposed by the government and the risks accepted in everyday life.

As some of you know, an IRB in Chicago justified -- actually, Dan didn't do this -- justified a protocol involving a clamp experiment -- induced hypoglycemia -- by noting that the risk of that experiment was less than playing on the sidewalks of the city. Certainly in Chicago, a lot of things would be less than that risk.

Precedent -- and this -- I have a whole list, but this will be my last. The precedent heuristic -- this is relevant to something that came up earlier today -- fairness, due process, stability and other values like that, tell us to give due weight to precedent.

But I think we're not -- this is not a judicial proceeding or process. Too much respect for precedent, especially when the history of cases is so short and probably too permissive, as in the 407 reviews that have been done so far, that can lead to underestimating risks or getting a distorted, I think, misleading set of standards and examples for what should be permitted.

So, yes, the government should do what three commissions or two commissions have recommended: let's find out, systematize. Yes, we should try to do something that David Wendler and Zeke Emanuel, which I insist, but let's not -- and I think the Commission should-- we're not bound by exactly what's happened in the past, as some Supreme Court might be. You have an opportunity to remind people of what -- the standards of ethics are not just standards based on what we've done in the past.

So, there are some of my reactions to what I think is already an impressive progress and sure to become an important and excellent report. Thank you.

DR. WAGNER: Dennis, thank you for your advice and your warnings, and we thank both of you for that.

I would like to see now, if there are questions from the Commission for either of you to address. Dan, did you want to talk about risks on the sidewalk, or -- oh, okay.

DR. SULMASY: I didn't want to talk about risks on the sidewalks of Chicago, which are unfortunately greater than they should be, but I did want to ask about your comment about assent and just clarify. Were you advocating, as I guess Allan Fleishman had, that instead of saying age specific, we use developmentally-specific protocols for achieving the assent of -- appropriate assent of children?

DR. THOMPSON: I was assuming that that was one possibility under consideration, and what I was pointing out I think is that it's possible to do something like that in the kinds of trials we're talking about with MCMs and that that would be better than following a rule which mainly we do now because that's the only way to administer it to a large number of people and for it to be unbiased.

But equally important is that whoever -- even more important, if we do that, is that the people who are securing the assent are independent of the researchers and have some expertise in being able to assess the developmental stages.

So it has -- it has a risk, actually, that the rule-oriented thing doesn't have, but I think it has a benefit that makes it worthwhile.

DR. WAGNER: Let me ask Tom to comment on that also. Assent of a child and consent of parents was something that you discussed when you were talking to us about Recommendation Number 6. Do you agree in the value of having independent assessors for obtaining that sort of assent to work?

DR. BEAUCHAMP: I think you need independent assessors throughout much of the system. I'm not even very keen on the IRB system, of how it works, because I don't think the IRB system has sufficient independent assessors.

Now, were you asking about the matter of assent more generally or just that one point?

DR. WAGNER: That one point, but please feel free to broaden, if you care to.

DR. BEAUCHAMP: Well, I would just add that the National Commission was powerfully impressed with some of the testimony that we had about assent of children. Now, that was 35 years ago, so we're talking about a long time ago, but there was a paper done by someone at Michigan or Michigan State. I forget -- I think it was Lucy Ralph Ferguson -- that powerfully impressed us in the empirical work that had been done. When the Commission uses the language of assent, which it does all over the children's report -- it's really all over the place -- it means that very seriously. It takes very serious the idea of, in many children, that capacity for autonomy. It's much less clear about how you go about assessing that, because it's relying more on its expert people than it is on its own judgment, but it was certainly a very important consideration.

DR. GUTMANN: Thanks, Tom, and thank you, Dennis. Both your comments individually and collectively were far more than a minimal increment over minimally helpful. They were close to maximally helpful for us really, and I'm just -- in an effort to get the maximally helpful, I'll ask a question to elaborate and clarify for Dennis.

I was really struck, among many really, really incisive and helpful comments, on your picking up the -- you clearly looked at our previous deliberations on our importing 406 more rigorous standards into 407, and not overly -- I mean they're rigorous, but likely to generate, you know, knowledge of vital importance, as opposed to a reasonable opportunity to address the serious problems.

And I just wonder if you could elaborate on your telling -- you know, advising us to give more guidance to the Secretary and panel, are you suggesting we not only emphasize how important it is to enforce the language of vital importance, but give some examples of what vital importance might be.

And I don't want to put words in your mouth, so what -- what additional guidance do you think we could give the Secretary that's within our competence to give?

DR. THOMPSON: Yes, I was suggesting some examples, but also categories. I think the examples are maybe easier, at least working at that level of abstraction, in the case of minor increase over minimal risk.

I mean, I -- you know, you could systematize those and give actual examples. Lumbar punctures -- so -- The seriousness of the research is -- the seriousness of -- I guess, it is the research -- involved something you were talking about this morning. Not just contribution to knowledge, but imminence of the threat. It's of vital importance because if we don't do it, there will be a terrorist attack and we won't be ready.

Well, you could just say "we'll leave that up to people who have more information than we do", but you could also offer some categories. I'm not suggesting these would be the ones that you would adopt or even that I would adopt, but you could say, or one might say, just the fact that an incident has occurred in the past, using anthrax in this case, once does not automatically mean that it will certainly occur in the future and that that should count as of vital importance.

That's not sufficient. I would say, maybe you don't agree, but it's a category -- an incident that had occurred once by a loner who was discovered, and all it shows is it's possible to do it, but it also shows that it was possible to discover it.

So, there's another category would be yes, if we have, Alex, capability and intent and it's very specific, we can't tell you exactly who it is publicly, but we know there is this active organization that has the capability and the intent to spread anthrax, even though it hasn't happened yet, that may count as part of the reason for vital research.

So what I'm suggesting is that -- and this is where some of the people who know more about security could help a little bit do categories.

Obviously you're not going to be able to define what imminence or seriousness is. So that's one part of it. Somewhat easier, would be, I think, to give some examples of how the research might be beneficial, of vital importance, which you've been talking about this morning.

It would -- but here, I would caution, you know, something that hasn't been talked about, the research will be relatively public, and the more, in some cases -- I don't think this is probably

true of anthrax -- but in some cases, extensive research done on some pathogens and vaccines, could be of benefit to some clever terrorist who could say, ah, now we know what vaccine they're going to use, we will make sure that our pathogens can bypass that.

So --

DR. GUTMANN: Be careful what you wish for.

DR. THOMPSON: Be careful what kind of research value -- to whom is the research valuable.

DR. GUTMANN: Good point.

DR. WAGNER: Tom, your thoughts on that?

DR. BEAUCHAMP: I don't think I have anything in addition to say. Thank you.

DR. WAGNER: Christine.

DR. GRADY: I want to also thank you both for a very provocative thoughts.

Tom, I wondered if I could ask you to comment on how the Commission thought about minor increase over minimal risk and why they didn't come up with a more -- a definition or a more useful way to think about it than they did, and whether you think they did it right, I guess.

DR. BEAUCHAMP: Well, I think I would agree with you that, hopefully, you would come up with a better way to think about it. Here's the problem the Commission faced. This was extensively debated, extensively debated, and we had at least two commissioners -- at one time it was pretty much an even split -- thinking that even something like minor increase over minimal was not going to fly, and yet we -- and we not only debated this pretty strict criteria greatly, but also went into example after example after example of progress that had been made in pediatric research, and the Commissioners were convinced that you simply couldn't cut it off at minimal reasonable risk. That that would be absurd. So what's in the next level that you can accept? And two commissioners were unwilling to accept anything beyond minimal risk, so this, then, became something of a compromise.

Also it's a bit of a punt. The Commission did two kinds of punting. One is in general, it punts a lot of stuff off to IRB. It doesn't decide -- I think a lot of the kinds of the thing that Dennis was talking about, you'd like to get clear on it, you debate it for hour after hour after hour, you can't get your group to agree, so you punt back to an IRB, and that's really what's happening in this case.

It's punted to an IRB to determine what this level is, rather than the Commission trying to do that in the abstract.

It's unfortunate, but who has been able to improve on it since then and get something like a consensus?

DR. GRADY: Can I follow up just a little bit, because Dennis offered a nice suggestion about giving some examples of what might count and what might not count as more than -- as a minor increase over minimal risk, and we've talked about that off and on all day.

DR. BEAUCHAMP: Yes.

DR. GRADY: We haven't spent much time talking about the examples yet, but I wonder if you think that's a fruitful way to go.

DR. BEAUCHAMP: If Dennis' suggestion is the fruitful way to go? Are you asking Dennis?

DR. GRADY: Well, I guess if you think, you both, maybe -- a lot of people said if we give more concrete examples, and you know, some of the dilemma for me actually of giving concrete examples is I hear often when we say sore arm for a minimal, and then we say liver biopsy for--, those are not similar. One is a reaction, and one is a procedure.

DR. WAGNER: Right.

DR. GRADY: So we have to be careful ourselves about how we would put things in the category and out of the category, but I guess -- I guess for both of you, do you think that that would be a helpful thing for this commission to do, to try to say, in this context, here are the kinds of things that we would consider in the category of minor increase over minimal risk, and then greater than that?

DR. BEAUCHAMP: If you can get agreement among your group, I don't know if you've tried to do this or not, we did address lots of cases and found -- very little agreement, I'm afraid. I think, Dennis, did you mention lumbar puncture? Was that the example that you used?

DR. THOMPSON: Yes.

DR. BEAUCHAMP: Based on one rather agonizing experience, just one, but one rather agonizing experience that I had with lumbar puncture for our son, I would not consider that minor over minimal.

DR. GUTMANN: I think we get agreement on that. Could I just follow up on this, because -- so one of the challenges of the minor increase over minimal risk is there's a debate as to exactly where to draw the line for minimal risk. So if you give things that are clearly minimal risk and then look to those things that some people would put as minimal risk but other would put on a minor increment above minimal risk, at least you're moving step by step from what clearly everybody will say is minimal risk to those things that some people will say are minimal risk, and other people would say are minor increment over minimal risk.

If you do that and then you say the things like lumbar puncture, or pick your example, but I'll take the example on the table, that are clearly more than minor increments over minimal risk, there's going to be a space in between that I doubt, as wise as this commission is, or maybe because we're wise and therefore diverse, we're not going to get absolute agreement on, but we'll make some -- some progress on. As long as it's controversial where the gray area is, we're only

going to be able to, I think, do about that -- about that much, but that's more than exists right now.

I had a different follow-up question for Tom or, and/or Dennis on this.

When we're talking about risk -- minor increase over minimal risk, or minor risk -- this becomes, am I right, that both of you agree that this becomes particularly important in the case of research on children who do not stand directly to benefit?

That is, there's the amount of risk that you impose in that case becomes a more weighted -- it's always weighted, but what the National Commission was articulating were a set of standards that applied not only to children who wouldn't benefit from the research, but also for children who would. That's correct, Tom?

DR. BEAUCHAMP: Yes, that's correct. And you're right, it's more weighty in the case you mentioned, yes.

DR. THOMPSON: Yes, I agree. And it isn't, as you said, Amy, earlier, it isn't -- it's balancing in the usual way. They're not actually on the -- this number of children versus this number of children.

The other thing I would say, though, that that's why it's so important to make sure that the concept of direct benefit doesn't begin to expand too much, because once it does, then it has an effect on the level of risk you're willing to impose.

If I may just say to Christine, I think not only should the Commission try to give some examples -- and I think you might be able to agree on some at this point -- there's been a lot of experience since the Belmont Commission, but part of the discussion in this part of the report should be making distinctions like you just made, which I think is very important, between the pain or the effects of the procedure, which are known pretty much to be certain. It's not a risk. You're going to get a sore arm. The shot is going to hurt. You're going to -- you know, most people get vaccinations and they have some sort of minor reaction.

Or at the other extreme, if you stay in the hospital, you're likely to get sick. Sorry. That's one thing. And then there are the risks of a drug, which are foreseeable in a certain number of cases, but those two things have to be distinguished, and actually you read all the reports and people run them together.

So that would be a contribution, some little analysis, some examples.

DR. GUTMANN: And making that -- not only making those distinctions just as categories, but recommending that those distinctions be made--

DR. THOMPSON: Right.

DR. GUTMANN: -- in any protocol and IRB or 407 discussion, because they're relevant to gaining informed consent.

DR. THOMPSON: Right.

DR. BEAUCHAMP: Could I make one comment about that?

DR. WAGNER: Sure.

DR. BEAUCHAMP: I suppose this goes back to the earlier question. When we're talking about examples and what kind of examples would be useful, one that I ran into recently -- and I won't go into the details of it, but I found it illuminating -- was a situation where the option for individuals in a particular location were, either to be day laborers or to be involved in Phase 1 pharmaceutical clinical trials. Those were the two options for employment, so to speak.

That was enormously interesting to me, how very much more dangerous it is to be a day laborer. So if you could -- this stuff about daily life experience and what's familiar to you isn't really very helpful until you talk about what it is precisely you're talking about.

DR. GUTMANN: Yeah, that, I think -- I don't know how many of us you can see, but there's nodding on that. That is just the -- it was well intended, but it was very unhelpful. Indeed, in one report when they were talking about minor increments, they used the example of how many kids play football.

Well, we now know how dangerous football is, and while this is a good example of the difference between what parents and local associations, private associations, can agree to, there is no way we could recommend to a government to ask parents and children to assent to the kinds of risks that we now know -- concussions and the risks of concussions imposed upon children, and that's part of daily life. It's not -- we have to be much more careful than that.

DR. THOMPSON: It is the case that currently under 102 that's one of the standards, right? Ordinarily encountered in daily life. So, maybe you should say don't accept that, I think. I mean, the alternative is in the performance of briefly --

DR. GUTMANN: Too broad, right?

DR. THOMPSON: Yeah.

DR. MICHAEL: Okay, this is primarily directed at Dr. Thompson. You made a comment about us being more definitive about 407 panel composition, and specifically you used an example of having more than one community advocate, which I thought was great. You had earlier mentioned that you liked, as one of the goods, our emphasis on community engagement.

You made one comment I didn't quite understand, and maybe you were just being humorous, but you said --

DR. THOMPSON: Trying.

DR. MICHAEL: -- about putting someone who is a child advocate on. I guess, did you mean an advocate that might be too biased towards basically agreeing for letting science rip and not being an advocate to protect the research rights of children?

DR. THOMPSON: Sorry. I'm glad you asked that. I was too quick. That was prompted by an HHS advisory committee recommendation to Secretary -- not the current Secretary. I think it was Thompson -- who the panel recommended that -- or the advisory group recommended that there be one public advocate, and that that public advocate should be from the children's defense group. You know, that sort of person.

I object to that. I mean, I think it's in the right spirit. There should be public representation or members of the public who are not experts, they -- you know, but they shouldn't be typecast. I wasn't so much worried about the bias one way or the other. In my experience, on some of these, the public advocates are actually more balanced and less biased than some of the other members, but they're typecast into this role and they feel that they're representing the public, so they have to always say the same things. Like George Ball during Vietnam, here comes Mr. Stop-The-Bombing.

They have to play a role, and so I -- that's what I was objecting to, that they're only -- that the idea that there be one representative playing this role, and that there only be one. Sorry.

DR. SULMASY: I was just going to take a stab at the sort of untangling the conflation of risks that we've talked about and see if, particularly Christine and Dennis, would agree with this. That I think often we run together, and the discussion in the literature often runs together, the risks associated with either the delivery of the intervention or the monitoring of the intervention, which are, you know, typically things that aren't knowable. It's an injection, it is a skin biopsy, and distinguish those sorts of risks, the invasiveness of it, for instance, from side effects of the intervention itself, which are less predictable, but we have to rely on previous experience with animal studies, adults, etcetera, for making those. I think perhaps if that sounds reasonable to you, that might be the way we could sort of disentangle those two.

DR. THOMPSON: Good. That's a very good suggestion.

DR. ALLEN: A quick question for Tom Beauchamp and then one for Dennis. Tom, I'm wondering how the historical context of your children's report might have been affected by the children's rights movement from the '70s and '80s. And then I also want to know, Dennis from you, when you talk about conflicts of interest -- well, you raised the question about the composition of panels and about independence, and I wondered whether your ultimate concern was, is our report aware enough, self-aware enough about conflicts of interest throughout this whole process, and in that connection, are you hinting that maybe we shouldn't be as trustful of government, or just that we should be conscious that there can be conflicts between doctors and hospitals and researchers and patients and subjects and researchers and big pharma and hospitals?

What exactly do you want us to focus on here, the general problem of conflict of interest or on the problem of community engagement or on the problem -- see, I'm just wondering what you actually were trying to focus our attention on by raising those concerns, most generally concerned.

DR. BEAUCHAMP: Do you want me to start? You're asking a historical question about whether children's rights, the children's rights movement or something like that in the '70s or '80s

would have been the kind of thing that would have affected our volume of research involving children. I think that's the question.

I don't recall that ever really having coming up. On the other hand, we were pretty much a mid-1970s group, might have been a little bit early. I don't recall children's rights specifically coming up, and certainly I don't recall representatives being available in our public testimonies.

On the other hand, it was impossible to be embedded in that particular time without being aware of the various aspects of the civil rights movement and what followed in the aftermath of the civil rights movement. We, after all, were formed -- I think people forget that you had the Tuskegee ad hoc panel in '72, you had the Kennedy hearings in '73, and you had the National Commission underway up and running in '74, and the things are so closely connected and were bound to have a huge influence.

DR. ALLEN: But just to note, then you were exactly in the midst of the children's rights movement, so unwittingly you may have been affected by it.

DR. BEAUCHAMP: Yeah, that's right.

DR. THOMPSON: Yes, I'm glad you raised that, Anita. I tried, I avoided using the term conflict of interest, because that was one of the -- because it's generally associated with financial conflict of interest. And the IOM National Committee, which I was part of, found lots of bad examples of conflict of interest in medicine and were really concerned about that.

I don't think, from what I've seen, that the panels -- I may be wrong about this, and maybe you'll want -- the 406 -- the IRBs and the 407 panels that have been constituted have any financial conflict -- or any serious problem about that. They may. What I was referring to is more commonly called conflicts of commitment. And, no, it's not that I distrust the government. I'm not now and never have been and never will be a member of the Tea Party. In fact, I'm more likely to trust the government than some of the scientists, actually.

What I'm looking for is people who are independent, including scientists, experts, public health people, security experts, or members of the public-- who are not directly involved in -- who don't have a stake in carrying out the research.

And that includes also who are not too sensitive to, you know, who haven't spent their life with vulnerable children, who have been experimented on. They're going to be overly sensitive to that.

We want people like you, actually, if you hadn't served on this commission, you could be -- some of my ideal members of this, or at least some of you could.

(Laughter)

DR. GUTMANN: I'm glad we've developed immunity from that call.

DR. WAGNER: Are there other questions for these two great resources before we dismiss them? Or I ask actually if either of you have any closing thoughts, having heard our questions to you, or wishing we had picked up on something you had said. Any thoughts, Tom, before we let you go?

DR. BEAUCHAMP: I don't think I have any profound thoughts, but I do want to agree with Dennis about one thing that just emerged there at the end, and that's about nonfinancial conflicts of interest.

I think nonfinancial conflicts of interest are everywhere, and among the worst that I've seen are university professors. They are absolutely blind to it.

So, this is something if you get a chance to work on, I would certainly encourage you to do.

DR. GUTMANN: Sounds like another report, Tom.

DR. WAGNER: Opening the eyes of the conflicted. And, Dennis, any closing thoughts?

DR. THOMPSON: No, and thank you for the opportunity. I think you're on the track for solving this problem and saving us from terrible consequences and not only minimal risks, but maximal risks. Good luck.

DR. WAGNER: We appreciate the wish of good luck from both of you. We certainly thank you for your time with us today, and want to thank you publicly.

(Applause.)

For those in the audience and those listening, I want to remind you that we're always open to your comments. Actually, offline you can -- outside of this meeting, you can contribute to comments online at our website, [bioethics.gov](http://bioethics.gov). Amy, do you have any closing?

DR. GUTMANN: My only closing remarks are opening remarks; that is, the preface to we will reconvene tomorrow at 9:00 a.m. and continue our discussion of pediatric medical counter measure products, and then we're going to devote our final session to discussion of future topics for the Commission's consideration. So, thank you all for being such an attentive group, and thank you to all the Commission members. Thanks a lot.

(meeting adjourned)