



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

**TRANSCRIPT**

**Commission Members**

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Amy Gutmann: Yes. And it is a segue to a discussion among the commission and everybody here who has any questions or comments. We have spent a lot of time thinking about how we should respond as a commission to the Advanced Notice of Proposed Rulemaking that's focused on the Common Rule. I will use ANPRM for short. Now everyone knows what we're talking about there. It is an opportunity. We were asked in the ANPRM to give our advice on this proposed rulemaking. And I've asked Barbara Atkinson on behalf of the subgroup who's been working on developing tentative response and everything we discuss right now is tentative because we need more time to hear and refine our own responses to give us an introduction not this subject which does have to do with pruning and budding. And it probably focuses a little bit more on the pruning but we're going to in our report go beyond that. Barbara, would you begin.

Barbara Atkinson: I would and I would just have to say my other subcommittee member was Raju, so he may have some comments too. We struggled a little with this because the advanced notice was actually over the notice period. As a commission we did respond. Our chair and our vice chair did respond, but we will respond here, but we also hope that we will move forward very quickly and the notice will actually appear very quickly. So our report is a little difficult to actually not be out of date by the time our report gets published, if you will.

Amy Gutmann: But the NPRM will have a period and we will be in time for that.

Barbara Atkinson: Exactly right. And it is so important that there are some issues that we really felt we had to comment on now. This common rule has really been in place for a long time and it really in 1981 was the last time there were substantial updates to it. There have been some other updates in between but really it's been over twenty years that there have been very few updates. It really is time to make some substantial changes. I should first say that we had the opportunity to review the suggestions to the ANPRM from a variety of really important groups. I'd say that AAHRPP, the Association for Accreditation of Research Protection Programs made a very strong comment. The Council of Government Relations for Research Universities made one that we reviewed. The AAMC, the Association of American Medical Colleges and then the Secretary's Advisory Committee on Human Research Protection made a lot of recommendations in response to this, too. So we reviewed all of those and either agreed or disagreed with some of them. What we chose to do in our recommendations here for discussion was to mostly comment on the ones that we thought were positive and to say in a few places where we didn't agree with them. So we came down to seven recommendations and I realized in preparing for this that we didn't make recommendation on harmonization. I'm going to suggest that we make another one. We did discuss it in our discussion in our draft. But what we wanted to be sure we did was really, as the letter which was prepared did, was try to look at the ethical basis as specifically as we could for each of these things. I guess I'd say for first principles we wanted to be sure that protection of human subjects was really paramount in everything we did. It wasn't just about making things easier for investigators. Although that clearly is something we want to be sure gets done. In a way that allows for better human subject activities if things are streamlined. Protection is paramount. The oversight should be related to the risk of the study so that the more minimal the risk, the less oversight. More oversight of higher risk activities could then be an area of concentration. And harmonization, even though it's going to be very difficult, is probably one of the most important things that need to be done.

Our recommendations: The first one was to reduce the time for duplicative reviews. So really trying to mandate a single IRB review for multi-state studies was suggested. We don't think mandating a single review is the most important thing, but actually doing whatever can be done to encourage single review. Almost all of the people that commented suggested that it might not be helpful to have multiple reviews from each individual site for individual study, but in fact that having varying degrees of answers to questions in an IRB review might actually not be helpful. Having one IRB is something that could help but should not be mandated as being the only thing essential.

We suggested restructuring of the research oversight to appropriately calibrate the review activities with the level of risk. I mentioned that before. That came in the suggestions of the ANPRM in three different areas. One was that if you really have an exempt list of activities you should look at what's on an exempt risk. What exempt research is, are things like surveys or could be even expanded to some surveys and some focus groups and some kind of things that really have no risk to the subjects being involved in them. That list of exempt activities should be looked at and probably expanded and then a category of minimal risk activities should be reviewed. They suggested that the exempt research could be reviewed just by the investigator himself or herself. We really don't think that's appropriate. We really think somebody higher level than that needs to review the exempt research. The minimal and lower risk studies again should be reviewed but only in the beginning. The continuing review for certain lower risk and minimal risk studies would not be necessary. So only a single review and clarifying that routine IRB review of exempt studies and minimal risk and expanded categories really are not necessary.

The ANPRM suggested templates for the informed consent itself. And we agree that making some standardizations to the consent form and some templates available would create a regulatory safe harbor and we would hope would discourage the use of indecipherable legal "boiler plate language"—I love that. Many of the IRBs are very long. The informed consents are very long - thirty or forty pages - mostly of things that nobody could begin to understand. Making a standardized consent that is reasonable that really is aimed for the level of the person who's being consented would be really important. Just to suggest templates we also don't think is appropriate. There are some things that need to be more than templates.

Issuing guidances rather than mandates we think is important to encourage appropriate informed consent. So guidance was suggested by many of the reviewers. The ANPRM was really in more of a mandating mode. We thought they should be more in a guidance mode. Developing flexible guidelines and procedures for informed consent that meet the needs of the scientists who are in areas not of clinical trials per se, but may be more behavioral or social science areas, more public health areas, and more hospitals doing quality assurance kind of reviews – need to have more flexible guidelines than those who would be used for the traditional clinical trials. Then again, I would just add that we, in our summary, didn't suggest a harmonizing suggestion, but I think we definitely need to do that in our summary, recognizing that it would be difficult, but we need to work to harmonize both within the United States for all of the agencies and worldwide to the extent that we can and the harmonization needs to have the ethical basis that we've already been discussing.

Amy Gutmann: Good. That's a quick summary. I'm open to comments, but let's start with Raju. See what Raju wants to add to that.

Raju Kucherlapati: I just want to add two comments. It was really a great summary. I think that all of the different groups that responded to ANPRM. Everybody looks at these from their own lenses. And our commission is probably no exception. And the commission looks at these and all of the proposals in light of the principles that we have articulated in our SynBio report. I think that's probably an important component. Because we consider the considerations that the commission takes are universal principles that can be applied to any types of research and that they'll also apply here, so that's a that we take. And so that's an important component and we indeed make such a recommendation at the beginning.

Amy Gutmann: Let me just remind people. Commission members know this by heart, but not everybody in the audience may know what the principles are because they're very—they really are quite comprehensive. Public beneficence, acting to maximize public benefits and minimize public harm including the duty to promote activities like scientific research that has great potential to achieve the public's wellbeing. Responsible stewardship, a shared obligation among members of domestic and global communities to act in ways that demonstrate concern for those that are not in a position to represent themselves. Intellectual freedom and responsibility encouraging creative potential used in morally accountably ways. Democratic deliberation reflecting an approach to collaborative decision making that embraces respectful debate of opposing views and active participation by citizens and justice and fairness distributing benefits and burdens across society in a just and fair manner.

Raju Kucherlapati: The other comment and other proposed rule is to change the way that we have consent to include future research. And this is an important issue and there are several responses to the ANPRM that sort of suggested that this may be difficult to do and this might actually reduce the protections for human subjects. But I don't know Barbara if you agree. At least my view about this is that the way that the current regulations are truly hindering our ability to obtain the maximum amount of information from clinical research and it would be great to be able to find a mechanism without changing the protections to still be able to obtain consent to use the data for other purposes. That also raises another important question that the commission needs to think about. What about all of the samples that have been collected so far that are in various types of repositories and they're also very valuable resources and we don't have a mechanism to be able to deal with them?

Amy Gutmann: So open for comments. Christine.

Christine Grady: Thank you, Barbara and Raju for working on that section. I had a question, primarily about things that we didn't—that the ANPRM mentioned that we didn't say anything about. One of them is this suggestion to have a central database for adverse events and unanticipated problems, and in that way to harmonize the system across the government. It seems compatible with other things that we've recommended in our report. It's also a way to provide information about what's happening to human subjects in research and so I wondered why we didn't say anything about that and I have just two others that I'll add onto this.

Amy Gutmann: And I think we can in this section, we do in another section of our now ongoing drafting of this. So we may—

Christine Grady: You may want to support it here as well.

Amy Gutmann: Need to cross reference. We need some cross reference.

Barbara Atkinson: And I do agree with it. I think it was an oversight on the harmonization. I think we under put in what needed to be here.

Amy Gutmann: Okay. Good.

Barbara Atkinson: So I do agree.

Christine Grady: So then just three other short things.

Amy Gutmann: Just.

Christine Grady: Just three.

Barbara Atkinson: Quickly. Three.

Christine Grady: A sort of statement of opposition to mandating single IRB review is one that I have a little—personally have a little trouble with. I don't like the word mandate and I don't think that that is what I would recommend either. But regulations have a certain force and so maybe making the regulations language that that's the default where that should be—I don't know how you encourage it without allowing—it's already allowed, but people aren't doing it. What should we do to recommend the regulations say something that allows people to do it in ways that they don't feel they're allowed to now.

James Wagner: Ordinarily—

Christine Grady: Yes. That's the—

James Wagner: Ordinarily we'd expect—

Christine Grady: But there are exceptions and there are things that need to be fixed like liability and things like that that you have to point out.

Amy Gutmann: You say that very quickly “like liability and things like that”. That's a huge issue and I'm just saying what the group has said—why the group has said this. Until you fix that to immediately mandate single sites without having prior fix the issues of liability is a real—it just—

Christine Grady: But why not recommend that the default should be one single IRB and there should be attention to resolving—

Amy Gutmann: It's a recommenda—

Christine Grady: As opposed to saying—

Amy Gutmann: But you said recommend. Rather than—

Barbara Atkinson: And maybe it is work toward it. I do agree that in the end we should have one IRB, but we are nowhere even close to being able to solve some of the issues to get there. So there's so much work to be done, so maybe it's somehow phrasing it can do the work.

Amy Gutmann: You're making a friendly amendment rather than saying we should endorse mandating single site IRBs.

Christine Grady: Yes. But I think the regulations should make it clear that it's a good idea and some of these things need to be fixed up. The other one is the exempt category. It seems like our stand on that is: you can't trust the investigator to decide what's exempt. And I think the reality is that we already are trusting investigators when to decide to go to the IRB. Determining what's exempt in different institutions varies from institution to institution so as I understand what's proposed in the ANPRM it's to have a system of registration so that all investigators doing anything with human subjects or specimens would register. Already that's a step up from what we're doing now and a registration system, of course it would have to be developed and this will take time and resources could have an algorithm in there that directs the investigator to either go for further review or not. Saying that we can't allow—we have to have review for every exemption, which the regulations don't currently require, is a mistake.

James Wagner: Registration also addresses current transparency recommendation as well.

Christine Grady: Sure.

Amy Gutmann: I mean—

Barbara Atkinson: Can I – just a comment—I guess it must be very institutionally different but in our place everybody would have to at least come forward for a review. Registration would be just duplicative of that. Maybe there are places where if you're doing anything with human subjects you don't have to at least once bring it forward. But I don't think the whole committee needs to review or even one committee member necessarily, but I think somebody more than a person ought to review any human subjects and put it in some category. Somebody who's not the investigator. That's a personal view and if the committee feels differently about that we can go with what the committee feels.

Amy Gutmann: Nita.

Nita Farahany: So thank you. This was incredibly helpful. I know that these are difficult to go through all of the different recommendations as well. I wanted to build a little bit on Christine's question about the mandating issue versus default. I was a little bit confused by this in the draft, primarily because it's not really spun out to explain what the issues are. So we have kind of a line in the draft right now about enforcement issues, liability issues, and implementation issues. I know we're piggybacking on comments that have already been made, but I think if we're going

to take the position that mandating is not appropriate because of these limitations, then it would be quite helpful to say what the specific limitations that we think are and then incorporate into the recommendation that we think we're supportive of a single site IRB so long as the following issues are addressed and specifically enumerate what those issues are. If those issues are addressed we would be supportive of a default single IRB recommendation.

Barbara Atkinson: Right. I like that.

Amy Gutmann: And that's in the spirit of what's here, but—

Female: Great.

Amy Gutmann: It needs to be specified. Dan.

Daniel Sulmasy: In a couple of places in this section and other sections in the report we used the phrase we would like to have "guidance" rather than regulation. And maybe the experience of others around the table is different from mine, but the difficulty becomes once there's federal guidance, it's almost always interpreted locally as regulation as put in sort of create the kinds of barriers that people complain about. I wonder whether that really helps us a lot to say guidance. As soon as it says that these are the things that we would suggest you do, then every IRB is going to demand that it be done and I don't know that it helps very much.

Barbara Atkinson: I don't know how to respond. Here guidance was—

Amy Gutmann: What are we talking about—?

Barbara Atkinson: I think it was mostly about the consent form.

Female: The consent form.

Barbara Atkinson: And what should be in different sections of the consent form.

Daniel Sulmasy: There are other places in the report that we used that.

Barbara Atkinson: Yes. So in the consent form, I think being able to say put in X, Y, and Z was the kind of guidance that people wanted. Rather than saying, there's a template, just fill in the words. Which is almost more prescriptive and less helpful if you will. But being able to have, in general what was in sections to me is real guidance and isn't regulation. Maybe it's regulation if you say everything that you put there has to be there, but different kinds of studies. We're talking about studies now that are so different from thirty years ago that people have never contemplated the kinds of social studies researcher quality assurance research that exists now.

Daniel Sulmasy: So maybe just in this section you would say guidance rather than templates? If that's the strength—

Barbara Atkinson: Right.

Daniel Sulmasy: Of what you're saying there. I think that would be a valuable, but it will still be in essence interpreted as a requirement and probably reasonably so if its good guidance. Yes.

Amy Gutmann: Yes. Anita.

Anita Allen: Yes. Barbara, I was interested in your discussion about problems with informed consent statements and the inevitable useless legalese boilerplate, I think you put it. Also concerns about overly scientific technicalities, but the problem that I think needs to be equally emphasized is a problem of over simplification because I'd seen one informed consent statement for example aimed at an eighteen year old in which viral vectors were described as similar to colds and kind of like a taxicab that drives the gene therapy. So we have to be careful about not making our informed consent statements so dumbed down that they have the unintended consequence of understating the risk involved to the subject. And I wonder if you'd given any thought to that side of the problem?

Barbara Atkinson: I don't really know how you address that. I mean you do want to have—

Nelson Lee Michael: I was going to say you usually like to address this is to have a test of understanding that would be culturally consonant with the research populations and this is something that my own group does overseas all the time because you have to take difficult concepts and put them into a different language and you need some assurance back that there has truly been an understanding of the consent form. So that's all that could be a playground for misadventure depending on how the depth of understanding is done, but there are at least some procedures that you could put in place to recommend those kinds of safeguards.

Anita Allen: I hope we'll do that.

Amy Gutmann: I would prefer. I think the stricter standard is clarity rather than simplicity. I've seen many forms that even you know a doctor or who's not working in that particular field would have a very hard time understanding because it's not written in as clear a way as possible. Also there's a question of priorities of what I would hope from and I think we should recommend from the template is those aspects of risks and benefits that are most salient and most probabilistic should come first and those risks that are highest either probabilistically or given the harm that they present should be presented up front and not down in page twenty in small print. I think you're right. You don't want—I don't think we want to argue for simplicity as in you can understand it if you have a third grade education but you're not understanding what the real risk and benefits are here. So it's clarity that takes—it's harder to write a clear consent form than it is to write a forty pager.

Anita Allen: Yes.

Female: It is.

Nelson Lee Michael: For sure. Yes.

Amy Gutmann: Other comments? Questions? Again, anyone in our audience who would like to comment please write it down. Yes. Lonnie—I see you--?

Lonnie Ali: Actually Christine—she actually asked and it was on guidance and mandates so she asked the question for me.

Amy Gutmann: Okay so could I just ask us to drill down a little on the single site IRB and ask anybody on the commission to comment on what are some of the present risks that need to be dealt with before we feel that it's comfortable for the protection of human subjects to have the choice of one IRB rather than going through multiple IRBs because I think that's the issue and I think it's the reasonable issue standing between us and say one IRB. One IRB is simpler. It's faster. It's more efficient. So the—let's hear the "buts," because I think we need to put those into our report because we have to focus on what's going to protect human subjects. So beginning with Nita.

Nita Farahany: Again, I'm supportive of us ultimately getting there.

Amy Gutmann: Yes. I think we're—

Nita Farahany: Yes.

Amy Gutmann: —in concert.

Nita Farahany: But one of the first issues is the issue of forum shopping. You see the mob where people go from site to site, state to state to find the most favorable laws. Even with a consistent set of guidelines and recommendations, different IRBs handle things differently and I think we need to make sure that forum shopping this doesn't encourage forum shopping to go to the kind of the least—

Amy Gutmann: Least strict—

Nita Farahany: Least enforcement. Least strict, least oversight. Second and a major issue is the issue of liability which we mentioned but don't elaborate on.

Amy Gutmann: Right.

Nita Farahany: And you know a single site taking on full liability simply by being the overseeing IRB is problematic if it really is a multi-site project.

Amy Gutmann: And it won't take on—

Nita Farahany: Right.

Amy Gutmann: De facto, it will not take on sole liability. If multiple sites are engaged in research and somebody wants to sue, they will sue all sites even if only one IRB agreed.

Nita Farahany: That's right.

Amy Gutmann: That's just the fact of—

Nita Farahany: That's right, but then the question is if there's something that if you have forum shopping where there is an IRB that has more lax standards than other sites have to defer to, and that IRB happens to not in fact be up to the same standards as other sites, the liability isn't just that they carry liability it's that other sites expose themselves to liability by going through that single site which makes some which makes other IRBs potentially resistant or other institutions resistant to having that site be the site. Now that might help us with forum shopping. They won't default to it, but these are kind of interrelated issues.

Amy Gutmann: Let me just read this comment because it's directly on this point and is it Joan Rackland? Would you just stand up? Thank you very much for this comment. I think you have very good handwriting so I think I will be able to read it: When discussing the issues surrounding a single IRB of record, should the commission consider making a statement about having the default position be a central or consortium IRB but not necessarily a commercial one? Given the many concerns about conflicts of interest, inability to adequately consider local subjects needs and inability to gauge remotely situated researchers ability to conduct—ethically conduct the research I would respectfully ask that the commission consider distinguishing between commercial and academically based review boards. Thanks. Thank you.

Daniel Sulmasy: I was going to emphasize one of the points that was just made in that comment that one of the reasons to have multiple sites is often to try to get different populations and those different populations may have differences that are sufficient that they make ethical differences and there ought to be if there is a central IRB some mechanism of getting local input into that central IRB and I don't think that's been worked out.

Amy Gutmann: And it's interesting to my mind and to the Commission's mind that the ANPRM recommends a single site IRB only for domestic research, not for international research which may or may not make sense practically speaking, but it's troubling ethically speaking because there are different communities in the US as there are in the world and an international project that's in France or Great Britain in an affluent highly developed infrastructure could be very different and just as protective as a multisite in the United States that has less infrastructure at some of the sites.

Raju Kucherlapati: Can I make a clarification?

Amy Gutmann: Sure. Please.

Raju Kucherlapati: I think Dan you're implying that the way that the current system is that it is possible to have different levels of IRB approvals, but for multi-sites there is only one approval. Right? And so that's important to recognize that.

Amy Gutmann: Yes. Yes.

Raju Kucherlapati: So basically all of these changes that individual IRBs—they have to be approved by everybody else. And that so that is the major issue.

Daniel Sulmasy: I'm not disagreeing with trying to streamline that process. All I'm saying is that when it's done—if it's going to be done by a single IRB we shouldn't lose all of the local inputs that go through this now cumbersome process that we're trying to fix.

Amy Gutmann: Christine I'm going to – then John and then we're going to adjourn for lunch. But go ahead.

Christine Grady: Just two additions to this issue. One is to recognize that in fact right now some multicenter studies are being reviewed by one IRB. So it's not like something that's never been done before.

Amy Gutmann: It's permitted now.

Christine Grady: It's permitted.

Amy Gutmann: It's not required.

Christine Grady: It's not required and it's not even I don't know if I would even say it's the default, but I would say that it's being done more and more as time goes on.

Amy Gutmann: It's not the default.

Christine Grady: No. Secondly a lot of people I do think the pickup on what Dan just said that there are local issues that need to be considered and a single IRB can't deal with that and I think my own view on that is that it's wrong on two counts. One is there are ways to bring local issues to a central place if that was important. The second thing is if an IRB reviews a study I think we all recognize that that doesn't mean that all of the ethical obligations are over. You know everybody involved including people at the various sites where the study will be conducted, whether or not the IRB was there, too have responsibilities and one of their discretionary responsibilities is to say I don't like the way this study is set up. I'm not going to do it.

Amy Gutmann: Although the realism of that—it happens. It does happen.

Christine Grady: It does happen.

Amy Gutmann: But there's institutional as well as individual responsibilities for activities that go on and I don't think that we want to say that the institutions should for the same reasons John gave earlier about you need both institutional protection and individual protection, we want to make sure that a single site IRB, that a single IRB really as you said earlier and Dan suggested takes into account all of the ethical requirements wherever the research is being conducted. That's going to be really important for protecting human subjects. John.

John Arras: I'm good. Anita raised all my issues. I'm just discouraged that she raised them.

[Laughter]

Amy Gutmann: I'm going to ask Dr. Atkinson to make concluding comments and then we're going to adjourn for lunch and reconvene at 1:30. So Barbara.

Barbara Atkinson: I just wanted to comment on the question from the audience about the—

Amy Gutmann: Yes.

Barbara Atkinson: The commercial IRBs versus the academic ones. And I think there's good data now to show that some of the commercial ones at least are very good IRBs and possibly better than some of the academic IRBs. I hate to say that but I think it's probably actually true. So I would hate to make that recommendation here. Absolutely. I think the very best IRBs should be whoever certainly would do a multisite study and it might or might not be a commercial one.

Amy Gutmann: What we want to ensure is that we have—we put forward a standard that is maintains the highest level of protection and does not and I think the spirit of what you're saying is don't have forum shopping for the least strict IRB.

Barbara Atkinson: Exactly.

Amy Gutmann: And that's in the spirit of the ANPRM and we need to elaborate on that. Thank you all very much and we will reconvene at 1:30.