



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

## **TRANSCRIPT**

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#### SESSION 4: NEUROSCIENCE RESEARCH AND DIMINISHED CAPACITY

DR. GUTMANN: Great, this panel is going to revisit a topic that we discussed in our last meeting as well, and that is capacity to consent in research. And first we will hear from Dr. Jerry Menikoff, who is the director of the Office of Human Research Protections in the U.S. Department of Health and Human Services.

Prior to this position, Dr. Menikoff was in charge of the Intramural Human Subjects Protection Program at the National Institutes of Health and previously he was associate professor of law, ethics and medicine at the University of Kansas. He has also served on the faculty of the University of Chicago School of Law, and he is the author of *Law and Bioethics: An Introduction*, and *What Doctors Didn't Say: The Hidden Truth About Medical Research*.

And he is somebody who very early on when I was making the rounds consulting about our Commission gave us very useful advice on a subject closely related to what he is now going to speak to us about.

Welcome, Dr. Menikoff.

DR. MENIKOFF: Thank you, Dr. Gutmann. It is a pleasure to be here. It is a privilege. So the question I was asked to comment on is basically what guidance is out there regarding determining when somebody does or does not have the capacity to consent to participate in a research study.

So let me start out with the regulations, and I'm mainly going to comment on the Common Rule, which is what my office administers, at least in terms of Health and Human Services.

And there is actually only one real provision. So generally a researcher has to obtain the legally effective informed consent of the subject or the subject's legally

authorized representative. So that handful of words is actually the core in terms of answering your question here. And furthermore, the regulations do then define who or when you can have a legally authorized representative.

So the bottom line is these provisions are basically looking to a legal determination. And the way they're interpreted is in general, assuming that research is taking place in the U.S., it is basically a determination that is made under the applicable state law. So the bottom line is do regulations key into whatever state where the research is taking place, and this issue of somebody being able to provide legally effective informed consent.

And so to tie it into the underlying concept you want to know about here, if somebody presumably does not have an appropriate capacity to make decisions that are necessary relating to deciding to be in one or another research study, then presumably as a state law matter, they should not be able to provide legally effective informed consent. So bottom line, that sort of in a very brief nutshell is what the regulations actually say. So let me now try to parse it out in terms of what guidance there is out there because bottom line I don't think it is actually that complicated an area, at least in terms of the underlying concepts.

How you then implement them and make specific decisions could be complicated. I mean that is why experts like Dr. Appelbaum and others who spend a lot of time thinking about this and how you do implement it.

Okay, so in terms of the underlying question, only OHRP itself has a little bit of guidance on this issue but actually not a lot, and I give you some hint on perhaps why it is the case.

There is one FAQ discussing what should be considered in seeking informed

consent from an individual who has diminished decision-making capacity. It briefly notes that the IRB and a researcher should have appropriate information about the condition that is relevant to the subjects that are being studied. They should be knowledgeable about that. It briefly discusses the issue of fluctuating capacity and because of that, you may want, for example, to get the patient when they have a higher degree of capacity to authorize to provide somebody who they provide a power of attorney or whatever it is to make decisions for them, so not a lot is said.

There is another FAQ discussing obtaining legally effective informed consent in the context of urgent care or some emergency care setting. It says a little more, noting you have to look at the ability of the subjects to process information, to ask questions, to consider the risks involved, which pretty much are sort of the basic things I think it does boil down to.

I actually checked with our staff. We actually don't get a lot of questions on this issue. Looking back about five years, they were able to pull up about three queries and two of them were sort of even marginal in terms of this. And what we will often do in fact is when we get questions on this, we will say here is what the regulations say, and we will often refer -- NIH in particular has a very nice "Points to Consider" document that is about 10 pages long entitled, "Research Involving Individuals with Questionable Capacity to Consent" from 2009. It actually was an older document that they more recently updated. And it goes through sort of all the issues.

Getting back again to the bottom line, if you went back historically, there was a time when people looked at as a legal matter competences as an all or nothing concept, and that has pretty much been discredited. It has been discredited a long time. My law and bioethics textbook, which was mentioned earlier, I mean I cite a fairly famous case,

Lane v. Candora involving a woman, an elderly woman, who was a little bit senile but a judge eventually concluded she actually had capacity to decide that she didn't want her gangrenous foot amputated even though she would die as a result of it. And the bottom line is if you actually talked to her and listened to her, she actually made sense. And that's the bottom line in terms of most discussions of these issues.

The NIH document spends a fair amount of time doing a nice job saying you want to do is assess the ability of the person to make a decision about being in a particular study and not look at again overall general cognitive ability. So, again, we will refer to this document.

I will also note very recently, in fact, in the last two or three weeks, maybe it has been a month or so, I don't know, FDA came out with draft guidance on informed consent. And it actually has a page or so, a page and a half, on impaired consent capacity discussing how to assess this capacity. It notes you have to look into things like is the individual able to understand the information, able to show evidence of a choice, that they are reasoning in a rational way, understanding the nature of the situation, all of that sort of thing.

So getting back to the -- and oh, and SACHRP, the Secretary's Advisory Committee on Human Research Protections, it had a subcommittee looking into issues involving enrolling decisionally incapacitated adults. It made a determination on a variety of issues, including on this one, and it pretty much endorsed the NIH document and the same concept that we're looking at, capacity to consent, instead of this prior notion of overall competence or incompetence. So I think it is pretty well understood in terms of what the underlying rule is that we're trying to implement here.

Getting back to this sort of core point in terms of maybe why aren't people asking

a lot of questions about it, one way of looking at it is that there are many things in research that are distinctly different from clinical care. But my suspicion in this area is there is actually not a lot of difference. The bottom line, whether it is a clinical decision or a research decision, you want a patient who basically has the appropriate capacity to think about the decision you are asking him to make, and they could reason about it. So all we're trying to do here is basically implement concepts that are already fairly well understood on the clinical side. And so you don't really need a lot more.

Again, in terms of how you actually implement it, this obviously is very complicated. The NIH document briefly gets into some of the tools that are out there that can help people actually assess somebody's ability to answer a particular question in terms of enrolling in a research study. But, again, that's one take on why I think this hasn't been that complicated.

Let me close with sort of a segue to a very different area, which is assuming you have made an appropriate decision about whether somebody has this capacity or doesn't have the capacity, well, if you concluded they did have the capacity, and it is correct, you are pretty good. You are in a good situation. I might though, getting back to interpreting regulations, once you conclude they don't have the capacity, we are now in an area, as you all know, where the rules are very unclear. There have been numerous bodies, including your own predecessors in terms of presidential commissions, which have spent a great deal of time and effort trying to create rules in terms of how are we in fact going to make decisions for somebody who lacks this capacity. And right now, well, comparing it to children or prisoners or fetuses, we actually don't have sub-parts in our regulations even addressing what the rules should be for decisionally incapacitated adults.

I will leave it at that.

DR. GUTMANN: Leave it with a big open challenge, right? Thank you. We will hear now from Dr. Paul Appelbaum, who is the Elizabeth K. Dollard Professor of Psychiatry, Medicine & Law and director of the Division of Psychiatry, Law and Ethics in the Department of Psychiatry at the College of Physicians and Surgeons at Columbia University.

Dr. Appelbaum is a research psychiatrist at the New York State Psychiatric Institute and an affiliated faculty member at Columbia Law School. He directs Columbia's Center for Research on Ethical, Legal and Social Implications of Psychiatric, Neurological and Behavioral Genetics and heads the Clinical Research Ethics Corps for Columbia's Clinical and Translational Science Award Program.

Dr. Appelbaum is also past president of the American Psychiatric Association and of the American Academy of Psychiatry and the Law. He has received the APA's Isaac Ray Award and is a member of the Institute of Medicine. Thank you for joining us today.

DR. APPELBAUM: My pleasure. So this is what I was asked to speak a little bit about, assessing decisional capacity, actually how to go about doing it. And I want to start by noting some overarching principles that I think are here in this process.

The first is that potential research participants, like all of us, are entitled to a presumption of capacity. And only in the face of evidence that they are in fact incapable are we -- can we legitimately take away their decision-making powers.

Secondly, when we do so, when we make that decision, that is a major deprivation of somebody's rights, and therefore we ought to be doing that with a great deal of care and even trepidation.

And, thirdly, whenever possible, we should avoid doing that so that when we see people who have some degree of decisional impairment, rather than jumping to the conclusion that they can't make decisions for themselves, we ought first to try to ameliorate their impairments so as to enable them to make those decisions before we turn those decisions over to other people.

Why do we need individualized assessment to do that? That is, why can't we simply identify categories of people who are so unlikely to have decisional capacity that we can simply rule them out as a blanket matter? And the answer is that if you look at the research, and I won't tick through all of these studies, whether you are talking about people with mental illness or people with Alzheimer's disease, there are data from other categories as well, there is a great deal of variability in decisional capacity looking simply at diagnosis, and that includes quite impairing conditions like Alzheimer's disease or Schizophrenia, which was what most people in the first study up there had. Nor do standard assessment tools really help us very much there.

And I've given you the example of some data on the mental state examination, which is used commonly in clinical settings for people who have some degree of cognitive impairment. If the scores are very low, it is true they are not likely to have capacity. If they are very high, they are very likely to have capacity, but you probably don't need to use the MMSE to find that out—you can just have a chat with them. It is that group in the middle that are the hard calls, and these instruments generally don't help very much there.

And so increasingly investigators, often at the behest of their IRBs, are turning to specific screening of research subjects in order to ascertain whether they have decisional capacity for consent to research per se, either because they are in higher risk studies, and

Helen Mayberg's DBS studies are an example there, or because they themselves are likely to be at higher risk of impairment and depending on the stage of Schizophrenia and the degree of acuity that we are dealing with, that group may be an example of folks about whom you would have a higher level of concern.

You can do this assessment in a number of ways. You can do it with a clinical interview but the data are not very encouraging with regard to the reliability of that assessment, although reliability improves if you give people specific criteria to apply.

You can do it with the symptom measures that we talked about earlier, but, as we said, those are not very predictive or you could use specific competence screening instruments, which is what I am going to focus on now.

And I'm going to tell you first a little bit about the usual conceptualization of decisional capacity that we apply in both clinical and research settings, and that most instruments are built around. We usually conceptualize decisional capacity as consisting of four elements. Does the person have the ability to evidence a choice? Can they say yes or no? That's the simplest level for somebody who is mute as a result of catatonia or comatose. There is no question that somebody else has to make the decision for them. But beyond that, do they understand the information that has been disclosed to them that is relevant to the decision that they face here, basically the nature of the research project, what is going to happen, the risks, benefits and alternatives to participation.

Thirdly, do they appreciate the nature of the situation in which they find themselves and its consequences? In particular, can they appreciate the effects of a decision about whether or not to participate in a research study on their own situation?

And then, fourth and lastly, can they reason? Do they have an ability to weigh risks and benefits and compare their alternative options in light of those risks and

benefits?

So those are the four elements that we typically look to in these assessments. And I'm going to give you examples of two tools that I think are probably the most widely, two most widely used right now, of which the first is the MacArthur Competence Assessment Tool for Clinical Research. And here I need to tell you that as one of the developers of that tool, I get about \$200 a year in royalties from it. So if you haven't bought it yet, by all means.

(Laughter.)

DR. APPELBAUM: It assesses the four basic elements of decisional capacity. There are a series of disclosures followed by questions and reasoning tasks. The MacCAT is individualized to a particular project so that specific disclosures are made that are project-specific, so it takes a little bit of work to develop a MacCAT for each project in which it will be used. And it takes 15 to maybe 20 minutes to administer, sometimes less, sometimes a little more, which in the research setting is not always an inconsiderable amount of time. It provides quantitative scores, which turn out to be highly reliable, but it doesn't give you a yes/no judgment. It still requires either the application of an individual clinician's judgment, taking the scores into account, or some sort of algorithm that has been pre-determined based on the nature of the project itself.

And this is an example taking from a MacCAT CR version for a Schizophrenia project of a disclosure. I won't take the time to read it all to you, but after a disclosure of one element here, the procedures of the project, we ask folks both to tell us broadly what their understanding is of what was just disclosed, and if they fail spontaneously to speak to the specific items within the disclosure, we then follow up with specific questions. Their answers are then scored on a simple zero, one, and two scale. Two is

they did great. Zero is they did terrible. And one is somewhere in the middle, they got some of it but not all of it.

The second assessment tool I just want to tell you about briefly is called the UBACC. It was developed by Dilip Jeste and his collaborators at the University of California and San Diego. That is mostly where it has been used, although it is published and it is occasionally used elsewhere. It is a 10 item scale. Their goal was specifically take the MacCAT structure and try and boil it down into five minutes instead of 15 to 20 minutes. It also has good inter-rater reliability and, as you can see, moderate item correlations with the MacCAT sub-scales. It has been used in nine studies so far that I've been able to find in the published literature.

And here are some of the sample questions from the UBACC: What is the purpose of the study that was just described? Do you believe this is primarily research or treatment? What makes you want to consider participating and similar scoring mechanisms?

There are reviews that are out there. I have given you the references to what I think is the best of them, although it is eight years old now, of the range of instruments that are available. These are the two most commonly used. You can use such instruments to set thresholds based on data from similar populations or based on an a priori judgment of how well people need to perform in order to be capable for your study. Where you set the threshold is likely to vary depending on the risk and complexity of the study. If they fail, the standard remediation is the best approach to take, and then they can be re-tested to see if their performance has been improved.

Finally, the question of who should do this screening is something that one of your predecessor organizations, NBAC, spoke to, and in their reports suggested

independent valuation, which turns out not to be all that easy to do. Who is independent? How do you get that person there when the subject is there? It turns out to be very complex. One of the advantages of the objective measures is that with a paper trail of people's responses and scores, you may not need to rely on independent evaluators, you could have somebody on the research team do it because it is auditable.

So to sum up, there may be, but it is not necessarily going to be, decisional impairment in folks with neuropsychiatric illness. You can screen for incapacity reliably and validly with acceptable costs. There are a number of instruments that would let you do that. And although we very much want to protect incapable subjects from making bad decisions, we need to balance that desire against the real societal interests in letting people make their own decisions whenever they can.

DR. GUTMANN: Thank you both very much. Open to questions from our Commission members or if there are any from the audience beginning with Christine.

DR. GRADY: Thank you both for nice presentations. I want to ask Jerry a question. Jerry, you said that the sort of controversy is what to do when somebody doesn't have the capacity to consent. But just a strict reading of the regulations sounds like it is fine to enroll somebody as long as there is a legally authorized representative that can give effective -- valid, effective consent. So I guess my question is my understanding, and I think a lot of people's understanding is that the state laws about who is a legally authorized representative and what a legally authorized representative can do in terms of decision-making are very variable. And so that creates a sort of at best a patchwork of what would be allowed by regulation in state law. And then on top of that, there is a lot of I guess the right word is disagreement about what is ethically

okay in terms of when to enroll people who can't consent for themselves. Do you want to say anything about any of those issues and Paul can too?

DR. MENIKOFF: Sure. I mean they are great issues. I mean on the latter issue, I think we are basically agreeing that what I was trying to get at was basically in terms of the ethical aspects of enrolling somebody once you've determined that they lack decision-making capacity. The current regulations don't actually give a lot of guidance other than vaguely saying they are a vulnerable subject. You need to somehow provide appropriate protections. Again, it is not as if there has not been a great deal of effort to sort of spell things out and to make things more uniform and NBAC, other groups, NERPAC, a predecessor to our current SACHRP Advisory Committee, have all tried to spell out these sorts of rules, often similar to the protections we have in Sub-Part D for children basically, which you could say, well, if minimal risk is okay as long as sort of the benefits to the subject might be equivalent to or outweigh the risks, that's okay. Then you get into the trickier area, well, if it is a minor increase over minimal risk, is that okay? And now you are getting into the realm that there are huge array of variations. As you know --

DR. GUTMANN: We know that very well.

DR. MENIKOFF: Okay. And in particular, for example, you could go to NIH's Clinical Center. On the side of the state law, again, this is the more black and white part; the regulations basically do rely on state law. They needn't have. I assume as a regulatory matter, this is a tricky legal issue whether under a grant provided by the legislation authorizing these rules, whether the federal government could have said we want to in these regulations provide a federal standard because we all benefit from this type of research and therefore this decision would be made as a federal matter. That is

not the current reading of the regulations. That is not what they say. It therefore does it leave it to each of the states.

Back in 2006 or '7, in fact, OHRP had put out a request for information asking should we change the rules relating to enrolling incapacitated subjects in research, and most of the commenters didn't want new regulations. Some of them wanted new guidance, but to the extent even any of them wanted new guidance, most of them wanted the federal government to tweak the rules in a way that would expand the ability to allow research in states that have somewhat limited rules. New York was one of the prominent examples at the time where it was very unclear under state law when you could in fact enroll a subject in research.

DR. APPELBAUM: I would just note that there is another option for incapable persons, and that is to rely on an advance directive that the person may have completed, which NBAC also talked about, and although not necessarily an optimal ways, but which is widely underutilized today. It really is almost vanishingly rare but could be a useful tool here, particularly for many of the disorders that are the subject of clinical neuroscience research today.

DR. GUTMANN: So that is a challenge that has come up before for us, which is how difficult it is to get more prevalent advance directives. And so you've raised it again.

Let me ask, there is a genuine puzzle I think, that you've raised that I think we could really -- we need to wrap our minds around and could use guidance from you. It is sort of a double puzzle because our subject is the brain. So Paul said, and very interestingly at the very beginning of your presentation, that the default ought to be to allow adults to consent, to allow them decide, right? And that is out of respect for

persons. They're adults. They are not children. They should decide for themselves. So on the one hand it seems like the presumption is in favor of consent, that's right?

Now, here is the other hand, when let's talk about not clinical -- not clinical treatment but research, so it doesn't stand to directly benefit the subject. When research goes awry and somebody has some cognitive impairment, is deemed to be not, you know, have some -- let's just put it, you know, not up to what is considered the norm, it is often seen as in the realm of a scandal that they were subject to research that they didn't stand to fully benefit from and they were assumed to be able to consent to but that is really questionable. So how do we reconcile these two things because on the one hand, I think what you began with, we all nodded, yes, it's depriving an adult of some capacity to consent to say you are not capable of it, but there's this other hand too. And that other hand isn't just theoretical; it is issued in a lot of public criticism of some research.

I'm happy for Jerry also to share the -- it's a genuine puzzle.

DR. APPELBAUM: So in some of the cases that most readily come to mind where scandals or purported scandals have erupted in the event of adverse outcomes, it has almost I think perhaps uniformly been true that no systematic effort to assess participants' decision-making capacity was made at the time of consent, which leaves us with a question mark. Did they really understand? Were they really capable of understanding? Do they appreciate what they were getting into, which could have been dispelled and could going forward be dispelled if we simply had a systematic way of doing it.

DR. GUTMANN: So that I think, and I will speak for myself because is the right answer to this, and it underlines what we have been calling for proactive ethical

standards where the proactive is so important because it is extremely hard after the fact, almost impossible after the fact to justify what was done if there wasn't a set of ethical standards and a practice underlying them. So I think your answer is spot on right, and we need to take that into account in what we recommend moving forward with neuroscience. I mean it is no different for neuroscience in the other, but there is this double whammy of it is the brain that we're researching.

DR. APPELBAUM: At the risk of --

DR. GUTMANN: Please.

DR. APPELBAUM: -- moving off spot on, I would just add one other piece here, which is that whenever we add protections, there are costs that go along with the benefits. And so I think what we need to do is to be clever about when we require those extra costs and those extra evaluations. So for significant risk research with impaired populations, absolutely. For a checklist survey that we're asking people to fill out, which essentially has minimal or no risks, maybe we don't need to go there.

DR. GUTMANN: Fair enough but, as we know, surgeons resisted the idea that they needed a checklist when they were doing surgery, and we know that surgeons using a simple checklist saves lives. So saving -- derailing science for the lack of a good instrument. We should certainly try to find one that is efficient in time and doesn't add unneeded costs, but I think we need one. And you have one. I mean it may not be perfect, but this is another case where the perfect shouldn't be the enemy of the good, so, yeah; I still think you are spot on.

DR. WAGNER: There are questions from the audience.

DR. GUTMANN: Yes.

AUDIENCE: One difference is that research is a contract not just, you know,

between the patient and the caregiver, but it is a contract between the physician and the investigator. So I think it is a little different than the patient care situation that you brought up.

The other thing is I wonder that the legal framework is not really relevant to what goes on in the real world. What goes on in the real world is, as was mentioned, there is concern when dealing with a patient with neurologic illness, is the patient really competent? Do we have really good evidence that that can happen? And the answer is we have some evidence. It may not be that good. So what people do is they go out and in this discussion the patient has been the focus, but that is not in the discussion for research consent, it is usually the patient, the family, so it is a group consent that you are really looking for. And I think when people do dangerous research, if there is not consensus in that group, among the family members; the general rule is you don't enroll a patient.

DR. GUTMANN: So I'm going to take that as a question. Do you agree that when you do research, there needs to be a general consensus in the family group and not only consent by the subject or the participant?

DR. APPELBAUM: Yes, I guess I would say that the more impaired the potential participant, the greater the value of pulling in other people to help him or her think through the decision and process it. But if you hear hesitation in my voice, it is because people have a right to make their own decisions even if they are disagreeing with their closest friends or family members. So I think we need to be careful about saying in a blanket way that we require familial consent. That seems to go against our usual approach.

DR. GUTMANN: And families, this is an empirical fact, are often divided in

these. So we should not think that family consent is in any way a simple -- you know, is a panacea for this. But still I think the point, the more impaired; the more one has to find a surrogate.

DR. APPELBAUM: We can think of them as helping with the process of decision-making, perhaps more than making the decision for the participant.

DR. GUTMANN: Yeah, good. Jerry, did you have anything you want to add?

DR. MENIKOFF: No, I would say getting back to your earlier "spot on" discussion, I would make the analogy to the regulations regarding children because basically, again it is a little different here, depending on the age of the child, but basically we require the assent of the child and the permission of the parent. And so you have built in some other person who we think cares a great deal of the person who is going to be in the research. And when we have reason to doubt that subjects themselves can make the decision, we build that in as a two part decision structure. And many have suggested should we use a similar structure for incapacitated adults. Again, to the extent that you are very clear that the person already has the capacity, that is less relevant, but to the extent there is doubt, that is the model we are using elsewhere. So it is not totally off the wall as long as your surrogate decision-maker is in fact somebody you really think will in fact be making a caring decision about protecting the subject.

DR. GUTMANN: This also underlines how important it is to recognize that consent isn't the only criteria for justifying research because there is also a level of risk which has to be taken into consideration as a necessary, not sufficient condition just as consent is a necessary but not sufficient condition.

Christine, you had another question?

DR. GRADY: I just wanted to say for the record, and I don't think you meant

this, Paul, but I'm just going to say it anyway. I think advance directives is a very good strategy, but it is an incomplete strategy for several reasons. One is a lot of -- it is hard to get people to write them. Secondly, often the most common form of advance directive is designating somebody, and then they become a legally authorized representative, and then we have the same problem. And then the third, of course, is that there are many people who are adults who never had the capacity to execute an advance directive.

DR. APPELBAUM: And since we're on the record, I just want to say I agree completely.

DR. GUTMANN: Other questions? Well, if not, we are going to segue into a roundtable so you will remain up there. And I want to thank both of you. We will take a break. We will take a 15 minute break.

(Applause.)

(Whereupon, a brief recess was taken.)