

**Third Meeting of the  
Secretary's Advisory Committee on Xenotransplantation**

Transcript

**Breakout Session: Working Group on  
Informed Consent Issues in Xenotransplantation**

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## PROCEEDINGS

2:00 P.M.

**MS. SHAPIRO:** Welcome to the working group on informed consent. Harold is making me talk because his excuse is that he's a good scribe. So fine. Maybe what we should do is to just go—well, first of all, does everybody still feel comfortable, having thought about it some since our telephone call, which I agree was very successful, does anybody have problems with how we have, at the moment, outlined our more specific tasks? Okay. Well, why don't we just start with number 1 and talk about what we've thought and/or what we've done and/or what we need to do in furthering each of these questions. If you all can find it, it's under tab 7. Actually it's the minutes of our teleconference.

So the first major issue that we identified—and by the way, I just jotted very few thoughts down in outline form, which I didn't get to all of you, but which is being copied for all of you, and Jim has some thoughts which we're having copied also, which should be very helpful probably on all these issues.

So the first is the definition of informed consent in the context of xenotransplantation. And Lilly and Harold were going to work on that. So I don't know which of you—probably you, Lilly, because Harold wants to be the scribe.

**DR. VANDERPOOL:** Can I be bold enough to pass around a document I've worked on that suggests some possibilities to the committee?

**MS. SHAPIRO:** Wonderful.

**DR. VANDERPOOL:** Now, I don't see these as—these are things Lilly and I can hammer out, but I think the group should have its run at these issues. What I've done in this statement is page 1 just said that—I'll just read the first paragraph.

“Clinically beneficial cellular, tissue and organ xenotransplants will depend on overcoming a number of scientific challenges, as well as responsibly dealing with a number of critically important ethical and legal concerns.”

What I do in the next two paragraphs is say that most of the discussion up to this point of these concerns deal with three or more issues, and the dots there express what these various issues are. And then I'm so bold as to say, in the fourth paragraph, “While ethical and legal overviews are valuable, the U.S. Department of Health and Human Services' Secretary's Advisory Committee on Xenotransplantation believes that more in-depth discussions and recommendations pertaining to selected and critical issues are necessary. This analysis focuses”—So see, what I'm doing is writing a prospective introduction, but please recognize all this can be destroyed, reworked or whatever.

“This analysis focuses on fundamental and critical issues inherent to the informed consent of prospective subjects of experimental xenotransplants. It will indicate how clinical research involving xenotransplantation raises basic, complex and, at points, new and controversial issues pertaining to informed consent. Before more extensive clinical trials begin, researchers and members of IRBs need to know what these issues are, why they must be dealt with, and how they might be resolved.”

Then what I do is just make a run at this first section that Robyn has introduced to us, namely, definition of informed consent. And I'll just read this through right quick.

“A description of the ethical foundations and functions of informed consent serves as a point of departure for the other topics discussed in this paper. “ And that's the idea of process and what all needs to be in there, and so on, and the special problems.

“What we call ‘the process of securing the informed consent of prospective research subjects’ easily conveys a somewhat vague activity and bland set of values. In fact, this benign sounding process reflects and upholds an essential and profound set of ethical and legal values.”

By the way, I decided not to throw in all the footnotes I could, so this is just straightforward.

“These immeasurably important ethical foundations of informed consent emerge when we ask why the process of securing informed consent of prospective research subjects is required before research involving adults can be initiated. The short and far from vague answer to the question, ‘Why is this required?’ is that it is legally and ethically mandated in federal legislation. The longer and far from bland answer is that informed consent preserves the values of self-determination, freedom of choice, human dignity, and protection from harm, abuse and deception. “

“The relationships between these values and the process of informed consent are depicted in medical codes, court cases, federal legislation, books and articles. The first article of The Nuremberg Code says, ‘The voluntary consent of human subjects is absolutely essential. ‘ Initially composed to bring criminal charges against Nazi physicians who conducted nonconsenting research on prisoners, this code’s accent on the free and voluntary consent of subjects functions as a way to protect research subjects from harm, deceit, fraud and force.”

“Regarded as the ‘quintessential’ summary of the ethics of research by U.S. federal agencies, the Belmont Report links protection from harm with the moral values of beneficence and nonmaleficence (not harming others). Belmont emphasizes that prospective research participants are primarily protected from harm through a thorough systematic harm-benefit analysis of all research protocols prior to their approval. “

“Although the Belmont Report does not link the process of informed consent to protections from harm, it views informed consent as necessary for the upholding of human dignity and the protection of prospective subjects from deceit and fraud. Informed consent upholds human dignity because consent is founded on the moral principle of respect for persons, which requires researchers to honor the freedom and autonomy of prospective subjects of research. These values are equivalent to the accent on the right of self-determination in U.S. law, which, similar to Belmont, holds that prospective subjects have a right to make free and autonomous ‘yes’ or ‘no’ choices with respect to their becoming or refusing to become involved in medical research. “

“Belmont furthermore describes how the moral foundations of the process of informed consent logically require three activities or action guides; disclosure of information on the part of researchers, and comprehension, and voluntarism on the part of prospective research subjects. The disclosure of information must be sufficient ‘such that persons can decide whether they wish to participate in the furthering of knowledge. “ That’s a quote from Belmont. “Each prospective subject’s comprehension requires a presentation of disclosed information that is adapted to each potential participant’s mental capacities, level of education, emotional needs, and social-institutional context. Researchers should also undertake measures that ascertain whether prospective participants, in fact, understand the information. “

“The third activity inherent to informed consent - the voluntarism or free choice of prospective subjects - requires conditions free from coercion, undue influence and unjustifiable pressures. The Belmont Report defines each of these actions that undermine consent and illustrates how they forbid such things as overt threats, excessive rewards or inducements, and the enlisting of close relatives for the purpose of obtaining compliance.”

“The process of informed consent is therefore founded on moral values and principles that comprise essential features of a moral community. These values are affirmed and upheld by the power of the law. They give rise to a number of morally required measures and action guides that expand upon the essential features of informed consent; disclosure of information, comprehension or understanding, and voluntary choice.”

So I just present that as a brief—and I don’t think we need more than a brief introduction of the theory behind informed consent, but you might want to change or alter these or suggest alternatives. And feel free to do that, but I just wanted to give this background so that we can take off from here to the other sections and really focus on them.

**MS. SHAPIRO:** I think it’s a wonderful foundation. Really is. Very well written. It’s so nice to have something to start with, isn’t it. It really feels good.

**DR. VANDERPOOL:** Thank you.

**MR. FINN:** Did good, Harold.

**DR. VANDERPOOL:** Thank you. To me we take these foundations, and we then apply them as we talk about what the process needs to be and what all the information that needs to be disclosed is and how it can be comprehended by simple information, not too long of a form, and what voluntarism consists of. And the question of voluntarism will probably help us deal with whether the researchers on the one hand or patient advocates on the other ought to secure consent.

**MS. SHAPIRO:** I'm just looking at our notes. Is it your thought then to specifically address what the PHS guideline says?

**DR. VANDERPOOL:** No, not really. The reason why I listed all those things that are required in the PHS guidelines is that when you get down to it, we're kind of locked into a whole set of topics, and I didn't even list the additional topics of what the Code of Federal Regulation requires, which is kind of general, all the risks and benefits, and some other things in addition to the PHS guidelines. So what we're faced with in xenotransplantation, for one thing, is a heck of a lot of information to disclose. And how will we do that succinctly?

**MR. FINN:** Diacrin did it with an enormously long form that I got.

**DR. VANDERPOOL:** That killed me, Jim, to read your form. I don't know how you understood it.

**MR. FINN:** I didn't read most of it. I read it after the fact.

**DR. VANDERPOOL:** That's interesting because you were going to accept what was offered without working through all that detail.

**MR. FINN:** I had no choice, Harold. I was going to die if I didn't do it. It was the last resort. So I went into the gates of hell willingly, and it turned out well.

**MS. SHAPIRO:** Are we going to talk about that in our paper, as part of the voluntariness aspect, about how many of these research subjects will be very ill and vulnerable?

**DR. RUSSOW:** I would take that question to be more under topic 2, the key components and characteristics of the informed consent process. As we said in the teleconference, a lot of these things are going to overlap. Seems to me that's the sort of issue that has to build on. The ethical and legal prerequisites puts it into more practical terms.

**DR. VANDERPOOL:** But Robyn's question and Jim's comments remind me of what is often said about patients with advanced cancer for whom standard therapy has failed, and the points that are made in the ethics of that literature are that cancer is coercive, and all you have to do is present the best possibility available for some remission and maybe cure, and patients are going to sign up. And that's what Jim's saying.

**MR. FINN:** That's right.

**DR. VANDERPOOL:** I mean if you're in a desperate circumstance, then your circumstances are forcing on you a decision, and the details are—

**MR. FINN:** Almost irrelevant—

**DR. VANDERPOOL:** -- almost irrelevant.

**MR. FINN:** -- when you're at that point.

**MR. BERGER:** It would seem to me that there's an additional question, the definition in the context of xenotransplantation. We're looking at informed consent as just being the patient. The thing that's different about xenotransplantation to any other kind of experimental surgery is that there's a public health issue, there's a

third party. So that's really the difference. We're not just talking about patient informed consent. We're talking about public informed consent. So that definition should include that, but this is different. It's patient and third party, not just the individual subject.

**MS. SHAPIRO:** So you're saying that maybe the introductory piece should also reference that there are unique aspects?

**MR. BERGER:** Well, that would be the major difference between this and other forms of informed consent.

**MS. SHAPIRO:** But I think your comment has two points. One is the close contacts, and the other is the community, and I see those and healthcare workers being in the first group, and then there's the bigger community.

**MS. KING:** To me what you're saying, I mean that's one of the major differences. I think the other is the commitment to long-term follow-up. And the thing that's concerning me—and I understand exactly what you're saying, and I would have done the same thing, but the thing that scares me about that is in making a decision to do xenotransplantation with an individual, we're talking about informed consent—they need to know what they're agreeing to—and what we're being told is, as in your situation and I think probably many others, people don't even care what they're agreeing to. They're just wanting the procedure. And we can't really ever assure—I know in some of the things we've looked at, it's like what should we do, testing to assure someone's going to maybe adhere? There's no way to predict adherence. There just is not. And the adherence literature will tell us that. So how do we ever get beyond someone just agreeing to the procedure and not even really thinking about what they're agreeing to post-procedure? Because that's so, so crucial to what we're talking about. The procedure is one part, but as you were saying, the third party consent and all the issues that can come from that, it's frightening.

**DR. VANDERPOOL:** What was your first point, Karren?

**MS. KING:** Well, Alan had said that he thought that the basic difference in this type of informed consent and others is the third party issue. And I said I think that's one. The other major difference to me, when I think of other informed consent procedures or other informed consent forms to other procedures, you don't necessarily have this long-term commitment to follow-up, and that's a huge part of what we're trying to, I think, ascertain and assure in doing this.

**MS. SHAPIRO:** Maybe, Karren, what we'll end up with in this document is not only, you know, hopefully some guidelines, but also recommendations which might involve long-term follow-up of the adherence issue as we get people into these protocols and what seems to work and what doesn't work and what the problems are. We just don't know. We can identify it as an issue and talk about it kind of, but we may not have the answer.

**MS. KING:** No, we don't.

**MS. SHAPIRO:** So where are we? I think we're on number 2. We're kind of spilling over into that anyway, which is key components and characteristics.

**DR. VANDERPOOL:** Robyn, one second. One possibility is to say that, what are the unique features of informed consent in xeno? And we've already said public risk, and then we've talked about the desperation of patients, which has some parallel in cancer research, but may be even the greatest here, and then lifelong follow-up, which means you can't withdraw. Once you consent, you can't withdraw. I mean do you remember the movie *Young Frankenstein*? When *Young Frankenstein* is going into the prison cell with the monster, and he says, "Regardless of what I say when I get in there, don't let me out of this door. Don't let me out. " And of course, the monster growled when he comes in, and so pretty soon *Young Frankenstein's* at the door going, "I want out of here. Open the blankety blank door. " It's like when you consent to lifelong follow-up in a desperate situation, and then let's say you get to feeling better, well, look, I mean you're in a different situation, and you can say, "I want out of here."

And then the other is the number and complexity of what must be disclosed. Now, it has to be disclosed. Why?

Maybe not so much for the voluntarism of the patient, but because of legal liability issues for researchers and institutions. You're going to have to tell what can happen. Otherwise, you're legally liable if you didn't mention what happened that happens.

So my question is maybe one way to look at this just besides the categories we have is to keep asking, What's unique about this? And that might give us a better outline than what we have. Actually it calls forth the outline we have because this number of disclosure, all those issues that the Public Health guidelines tell us have to be talked about.

Now, one thing that's not on that list of things that we've already mentioned is what Robyn was emphasizing in the meeting this morning when the issue of confidentiality came up. Because I mentioned to Robyn, I said, "You know, given these databases and given the specimen archives, is confidentiality seriously breached?" And Robyn's answer was, "Yes, but you've got to do more than tell people your confidentiality may be breached. You have to also say, 'and these are the risks that you face. ' " Right, Robyn? Do you have comments about that?

**MS. SHAPIRO:** I think that that's exactly right. And that is a difference that we should add to the list.

**DR. VANDERPOOL:** So another thing unique would be worries over confidentiality. I mean the biggest worries over confidentiality IRB faces at the present time is every time we have an issue that has a genetic component where this is going to go to some genetic registry. And xeno is going to have several registries, specimens, database. And you know, we've got to say, don't we, that we've got to hear from Eda and others about who can have access to this and how vulnerable that information would be because that's in some way going to have to be put into a consent form.

**MS. SHAPIRO:** I agree. Another thing—and I don't know if this is captured by your first bullet point about public health or not—is involving your family in the consent process in a different way than is usually the case. I mean the public health thing involves both confidentiality and, I think, consent of the family or close contacts or whatever you want to call them.

**MS. KING:** And when we say informed consent of the family, does that mean that if the family does not do the informed consent, that the patient would then be banned from getting a transplant? That's a whole 'nother part of that, which is very unique. I don't know of any such—

**MS. SHAPIRO:** Right.

**MS. KING:** -- except organ donation. The patient's not there at the time to agree. But that's really unique.

**MS. SHAPIRO:** Yes. And I think that that's an issue that we need to make a recommendation about.

**MS. KING:** So it's not only informing the family, but that the family can actually, by lack of consenting, kick the patient basically off the xeno list.

**MR. BERGER:** You can take that further because it could be future contacts, not just that on the spot might have to—someone remarries or they have a new close contact. They may have to sign their own form because they have to participate in the same process because they're in this for life as well as the patient.

**MS. SHAPIRO:** So they can't get married.

**MS. KING:** I thought of that too. I was reading this. How do you control that?

**DR. BLOOM:** Thanks. I'm not part of the working group, but we actually thought a great deal, both in writing the FDA guidance and in writing the PHS guidelines about the third party consent. And as both of the documents stand now, we don't ask for third party consent. We ask for third party education and notification. That was very intentional. If you guys want to make a recommendation that there should be third party consent—and Robyn's the attorney here—I would think that that would run into the legal issues about the

patient's autonomy.

**MS. SHAPIRO:** Uh-huh.

**DR. BLOOM:** Yeah. Okay. So we intentionally didn't do that, but that's within your prerogative to recommend it.

**MS. SHAPIRO:** I mean it would infringe on their freedom of choice to enter, but the response would be you're just not eligible unless you can do X, Y and Z and come up with the consent of your family. I mean I don't think it's a legal prohibition. Would it impact on our notions of patient autonomy? Yeah. But I don't think it would be legally prohibited if we were to make that recommendation.

**MS. KING:** Eda, when looking at your guidelines, if I remember correctly, the family was to be informed, but it was really up to the patient, correct?

**MS. SHAPIRO:** To inform, yeah.

**MS. KING:** To educate the family. Did you ever do anything to ascertain if the patient actually did that or it was just a recommendation to the patient?

**DR. BLOOM:** Well, the guideline just became final this year. The way we ascertain that is we ask that sponsors include in their IND applications items addressing "we will ensure that the patient's family is educated and informed. " We don't go further than that.

**MS. KING:** So it wasn't just that the patient was to inform? The way I read it was the patient was informing. But you actually asked the sponsors to ensure? So hopefully they were involved in that.

**DR. BLOOM:** Right. The sponsor is supposed to provide whatever help and means the patient needs to do that.

**MS. SHAPIRO:** But if the patient would just say, "I did it, " there's not necessarily any oversight about it.

**DR. VANDERPOOL:** Eda, I may be wrong about this, but as I recall the first draft of the guidelines, the patients were going to do most of the education and informing of the relatives, and then there was a lot of commentary received about that, and so now the guidelines say the patients are going to have some counselors and support people who are going to work with family members. And it seems to me that's essential because to have a desperate patient with all the burden of educating the family members about ten pages of material is just hopeless.

Now, to pick up Alan's question, let's say you educate, the counselor educates the family about what all they're going to have to do in terms of protected sex, and you can't give blood or you can't give blood donations. Presumably the family is going to go along with them, but what if the family, for whatever sets of reasons, said, "We're not going to give those samples, and we're not going to do that? " Does that mean this patient doesn't get a transplant?

**MS. SHAPIRO:** I think that's what we need to think about.

**MR. BERGER:** I mean to go on to your point, education wouldn't even be close to enough if in fact you're going to monitor family members, which is what the guidelines call for. So they would have to sign their own consent. And personally I would say, frankly, if you can't make it mandatory for everyone, then this whole discussion is moot to me because a voluntary basis on a public health risk is not acceptable.

**MS. KING:** Then how do we deal with the other point you raised? Let's say we do all of that. We require everyone that's in close contact now has to agree and sign and whatever. But there's going to be other future contacts if the transplant is successful, and there's absolutely no way we can mandate that those people in the future do anything. So we can cover our bases as best we can, but that doesn't assure, from a public health risk,

that they can ever always be covered.

**MR. PHELPS:** And it's too late at that point to exclude the subject from the protocol.

**MS. KING:** Right. It's done. It's a done deal.

**MR. PHELPS:** Right.

**MS. KING:** Just like legally what recourse would we have if the patient decides to say, "I'm doing better now, I'm not going to do this?" "We may mandate it, and we may mandate the family to do it. But legally what could we do to anyone who subsequently changes their mind and says, "I'm not doing it?" "What would happen?"

**MS. SHAPIRO:** I think the answers are different for the two different things. I mean for the first one you're right. I mean without identifiable third parties, we can't mandate them to do anything, which is not to say that it isn't worth it to make as exclusion criteria for initial participation that you get the consent of everybody who we do know about. And the second thing is, you know, then I think we've got to fall back on the public health responses if we really believe that it's a communicable public health risk, the public health responses, which include, I suppose, things up to and including quarantine.

**MS. KING:** If someone refused?

**MS. SHAPIRO:** If they said, "yeah," and then they decided not to. And we'll get to this later, but the federal regulations require, as part of informed consent, that you include their right to withdraw. So unless we're going to change those up front and say, "no, actually you don't have a right to withdraw," we have to fall back on, okay, if they do, what is the response?

**MS. KING:** The response would be now quarantine? Is that what you're saying? That's the precedent now?

**MS. SHAPIRO:** Or whatever other public health measures there are out there to take care of infectious dangers.

**MS. KING:** What is out there?

**DR. BLOOM:** As far as quarantine, I wish Louisa were in here because that would be a CDC thing, and she would know more about that by far, but it's my understanding that quarantine has to be a very clear risk. So just because somebody—

**MS. SHAPIRO:** Right. Oh, yeah. I mean this is presuming that we know more than we do at the moment about the nature and—

**DR. VANDERPOOL:** So picking on what you say, Eda, you could say to the family members, "It's very unlikely that quarantine will occur. If it does, it will be upon requirement by the Center of Disease Control." Okay. But let's say you say that, and so it's a distant risk, but the family member says, or say the spouse says, "Look, I'll go with the sampling, but I'm not going to be quarantined. I'm just not going to do that" So I assume you'd have to get full consent from the family members. But this raises an interesting philosophical issue, and that is, are the family members being unduly pressured? I mean if they're giving consent, because then it's supposed to be voluntary, and you come in and say, "Well, we're not going to give your spouse a xenotransplant unless you sign this form," that goes precisely against what Belmont Report says, that you cannot enlist a family member to put pressure on a patient to get a procedure. In this case it would presumably be wrong to use the patient to put undue pressure, if not coercion, on the family member to sign the form.

**MR. BERGER:** Yeah, I would agree. It would seem to me there would be separate forms, that a family member and an immediate contact, a close contact, would need to sign their own form and be educated separately, not from that patient.

**MS. SHAPIRO:** And if not?

**MR. BERGER:** Personally to me there is a public health risk. I'm not personally comfortable with that.

**MS. SHAPIRO:** So that the subject would be excluded?

**MR. BERGER:** Yeah.

**DR. COLLINS:** I'll tell you how we do it to give you the perspective—and Karren would know about this—of human transplantation, allotransplantation. Although the patient, let's say for a kidney transplant, the patient consents, the whole family has to buy into it. We look at each organ as kind of a precious natural resource, and we don't coerce the families, but they certainly have to buy into the whole process. And they're going to bring the patient to their appointments and that sort of thing, and if a patient doesn't have a car to get to follow-up appointments, then they're not even listed. And just looking at the point that you were making, Dr. Vanderpool, if the family does not buy in and they don't say that they're able to participate, then they don't even get as far as being listed.

**DR. VANDERPOOL:** The person doesn't even get put on the waiting list if the family doesn't agree. And you try to preserve the family members' voluntarism to some degree anyway in that, right?

**DR. COLLINS:** Certainly that's the case. We do that. But when we're talking about getting someone on the list, they have to have advocates, multiple family members with them. This is especially true for liver transplantation where a lot of the disease processes are self-induced. They have to have an incredible support system. The family has to buy into the process before they even get listed.

**MS. SHAPIRO:** The difference, though, is the rationale behind it. For yours it's you need the support network so that the patient will do well.

**DR. COLLINS:** Right.

**MS. SHAPIRO:** And in this thing we need them to agree so that the rest of us will do well.

**DR. COLLINS:** I guess the point I'm trying to make, Robyn, is that if they do say no, then we'd have the opportunity to say, "Then no, you can't get the xenotransplant," which may not be fair.

**MS. SHAPIRO:** So where are we?

**DR. KIELY:** I think we're sort of getting into 2. I think we've gotten to 2.

**MR. PHELPS:** I think that Dr. Vanderpool has given you a very good introduction. He has skipped over the ethical stuff. Other people have written about that. He's gotten to the nugget of what informed consent is, and you've laid out here several ways in which xeno consent is different from other kinds of consent, and that's the outline for the rest of your paper. You're just going to touch on each one of them. Most of those you already had on your list, but we'll have the rest of them so that you don't miss any new ones here.

**DR. RUSSOW:** Just one last comment. Although Dr. Vanderpool concentrated on—

**DR. VANDERPOOL:** Everyone call me Harold.

**DR. RUSSOW:** Okay.

**DR. VANDERPOOL:** I'll try to call you all "Dr." in the meetings.

**DR. RUSSOW:** Yeah. Harold concentrated very well on pretty specific issues. Since I didn't give Harold my outline before the session—and I should have—I did in fact focus on some of the more basic ethical issues. So that can be a part of it. I'm sure that I've gotten way too long-winded about it.

**DR. VANDERPOOL:** Tell us some of these, Lilly, that we need to deal with. And of course, Robyn has an outline here also. So we need to get the full grid so we can write our book on Xenotransplantation Informed Consent.

**DR. RUSSOW:** Well, before I do that, I just wanted to suggest in the introduction to the whole report that we acknowledge that there are important ethical issues that we have not addressed here because of our specific focus on informed consent, and we might even give a few examples just so that people don't think that we've forgotten about them.

**MS. KING:** That's a good idea.

**DR. RUSSOW:** Basically when I was looking at the ethical foundation of informed consent, I started with the Belmont Report's emphasis on autonomy and then sort of traced back or sort of tried to expand on the notion of what autonomy means and what it requires. And I've got a bunch of subheadings under that. But basically arguing that since autonomy is at the core of our guidelines, we need to use those considerations as the basis for determining what informed consent must or doesn't have to include. So I get into the whole utilitarianism versus respect for persons issues. I could do that in a paragraph or I could do that in a book. But I thought that that would be important as the introduction to the whole concern of informed consent and give a foundation for our answers to part 2 about what the key characteristics and requirements are.

**DR. VANDERPOOL:** Which would mean this introduction needs to maybe have a separate, albeit hopefully somewhat brief, paragraph on autonomy. You're talking maybe the philosophical type of things. I try to address that, but I don't really define it as not using persons as a means toward an end, but rather, as an end in themselves.

**DR. RUSSOW:** Yeah, that was going to be the main theme of my description or my contribution if you wanted. Again I just wanted to clarify that in the sort of general introduction to the report that's when I was talking about acknowledging issues that haven't been addressed. When we start discussing autonomy and its role in forming a foundation for informed consent, that that be part of part 1.

**DR. VANDERPOOL:** What you have is the legal tradition really leads the philosophers in terms of history. The court cases say persons have a control over their own bodies, and so it's battery if you're treated without fully consenting to any medical procedure, and the medical ethicists, bioethicists and philosophers, pick up that right of self-determination and argue it in terms of philosophical roots of autonomy, the right of free choice because. But we could maybe specify a little more that there are two traditions here. One is legal, and one is ethical. And both of these are accenting the same notion of self-determination is the language of the law, and autonomy is the language of ethics, but they amount to the full right of voluntary choice to accept or refuse experimental treatment. Does that make sense?

**DR. RUSSOW:** It does. And I haven't addressed the legal issue and how the interplay between law and ethics gets played out. I do suggest, however, that autonomy and respect for autonomy and respect for persons as rational agents requires more than just giving voluntary consent. It requires giving consent to something that one has understood clearly enough to make a rational decision. And what that requires is, to a large extent, up to the individual patient. So for example, your discussion of the Catholic tradition and the Catholic response this morning, which was very clear and very good, might not matter a darn to somebody who's a Muslim or somebody who's an Atheist. Insofar as the report emphasized rationality, they might be interested in some of that, but not all of it, because you start reasoning from some basic presuppositions that not everybody holds.

**DR. VANDERPOOL:** That, Lilly and group, raises an interesting issue about what all informed consent and what all voluntarism is. I say there that, you know, as Belmont points out, the three elements of informed consent are disclosure of information, comprehension, and voluntarism. Okay. And comprehension usually in the discussion of ethics is said to be something that the researchers have to double-check, have to check or make sure that they understand what's being disclosed. Otherwise, they're not getting fully informed consent. Right? Okay.

Now, to take Jim's statement, would it be a form of coercion to say to Jim, "Look, you're not interested in these 20 pages where we tell you what all you need to know about what you're getting into, and we're not going to give you any treatment until you show that you comprehend 20 pages of information, and we're going to give you some verbal, an otherwise test to make sure you understand it because if you don't understand all this information we're giving you, you haven't given informed consent?" "Okay. Well, that would mean that there's a certain amount of pressure—maybe undue pressure—to comprehend all this information.

Now, from Lilly's standpoint, if you have to make a rational decision—and this is what Brook Brody argues in the last issue or so of IRB—Brook Brody says that to get fully informed consent, you need to find out what a prospective subject's value system is—Brody probably doesn't want me to describe his position this way, but this is what I got out of it—what his value system is and make sure it's aligned with this yes or no decision the patient's making. And so you don't care what the value system is. It can be Catholic, Buddhist, Atheist, Hopi Indian or whatever. But the value system needs to be there and needs to sort of fit in with the patient's decision.

Well, one way to look at this from the standpoint of a libertarian is to say, "You have a right not to comprehend a lot of things, and you have a right not to have your value system pried into, so we'll make sure it lines up with the decision you're making because that's paternalistic. Jim, we have to talk long enough for me to figure out what your values are and make sure that they agree with this decision you're making. That's terribly paternalistic. So I'm just talking about a philosophical concern I have, and to me I take the morally paternal view, and that is patients ought to have all the counseling they want, all the information clearly specified, but if they decide not to read all of it, not to speak of not fully comprehending it according to our check markers, then they can still go ahead and make a decision. But see, that doesn't agree exactly with Belmont where they're supposed to comprehend before they can make a voluntary choice.

**MS. SHAPIRO:** Because he comprehended. I mean it's not just a privacy thing. It's not trying to fit his values and being sure that they're aligned. He comprehended that he wasn't going to—I mean he comprehended his decision not to get into all of it because he had something else in mind, and that was to do whatever he could do; am I right?

**MR. FINN:** You're right. Absolutely correct.

**MS. SHAPIRO:** So our obligation to respect his autonomy is to accept his comprehension of his decision not to know more. That's what I think. So I think it is consistent with Belmont.

**DR. VANDERPOOL:** And what you're saying, Robyn, is even though the consent form has all this information that many people, particularly all of us OCD, obsessive-compulsive people, we'd want to read it all and comprehend it all and then make a decision, but not if we're as sick as Jim was. So some people aren't OCD, and they just want to get a general picture and then say, "Hey, go for it. "

**MR. FINN:** That's exactly what happened in my case. They presented the facts, I listened to what I wanted, I made my decision, and so be it. I'm very cut and dry. I don't get into fancy details too much. I want to know what's going to happen, and then I make a decision based upon that information. And that's what I did. And in my case I'm glad I did.

**MS. KING:** I don't want to play the devil's advocate, but is xenotransplantation different because of the public health issues involved? If the comprehension is, "I don't want to comprehend all of this, I just want to have this procedure because I want to live, " but we're saying they need to comprehend what it involves for their long-term follow-up, not only for themselves, but for our public health interest. So to play the devil's advocate, can you carry what you're saying? And I'm more inclined to agree with what you said earlier on too. It's up to them to decide how much they want to know. But in this case do we have a different obligation to society?

**DR. VANDERPOOL:** Karren, I have a possible compromise, and that would be that we could say in our informed consent statement that there has to be proof of comprehension of the public health concerns and a voluntary choice to accept these terms—otherwise, you don't have leverage later on if they decide to drop out—but on some of the other matters that are going to be detailed, you don't have to have proof of a full comprehension of everything. What I'm wondering is whether you have to have comprehension on certain

things—and we’re going to have to stick by our guns on that—but then say informed consent that respects the persons. And the Belmont Report uses the phrase, “for whatever your personal reasons are and whatever your personal desires are, we honor that. “ To respect people means to respect your reasons for making your decision in your own way.

**MS. KING:** I feel comfortable with that. I guess the only thing I would say is just to be very aware of—and I speak from experience with the dialysis and transplant population. I don’t want to do anything that gets providers off the hook to provide the education because the medical healthcare field is rampant with paternalism and lack of educating patients in general all across the board. I don’t know if you would agree with that from your perspective.

**DR. COLLINS:** I would agree. I’m guilty.

**MS. KING:** But I think that especially in today’s healthcare system with decreased staffing, et cetera, there’s a lot of reasons for that. But I think we want to make sure that in saying that, we don’t give some providers then leeway to go, “Well, we didn’t need to educate them that thoroughly because they really didn’t want to know. “ So I’d caution us against doing anything that would allow that to happen, to leave it up to the patient to choose, not the provider to make the decision, “Well, you can’t comprehend this, so therefore, I’m not going to tell you.” That happens all the time.

**MR. PHELPS:** It gets harried to start drawing lines because then you get into the whole question of who draws that line? Where does the line fall in this case?

**DR. RUSSOW:** Although it has, you know, a strong philosophical basis. And I think you’re right about all of the things that you said and that Jim has said and all the other concerns, but I think in a purely practical way—and that’s when I get into my contribution to part 2 -- in a purely practical way there may be ways of devising what I would call a multistage information process. So there are some things that are absolutely basic that everybody has to know at least in general outline. And then they can request how much additional information and how much detail they would want before making a decision.

**MS. KING:** As long as they know what to ask. And I think that’s often the problem. With new patients, for example, with dialysis or transplantation, they often don’t know what to ask us because they have no clue what’s happening. So they have to know how much there is to know and how much they need to know before they can even make that decision.

**DR. RUSSOW:** I agree entirely, which is why I said there are some basics that are going to have to be required. And in effect they’re telling the patient or the prospective patient what sorts of things they might really want to think about and ask questions about.

**MS. KING:** They’re told about everything, but how detailed it goes would be up to them to ask.

**DR. RUSSOW:** Yeah.

**MR. FINN:** In defense of the process that I went through, I was given very demanding psychological tests to make sure that I was capable of comprehending what they were asking of me. They didn’t just throw me in the OR, in other words.

**DR. VANDERPOOL:** You’re saying you were, Jim?

**MR. BERGER:** Excuse me. The process took how long in order to go through informed consent?

**MR. FINN:** Took about six months from the time I first learned about the operation till I had it done, about six months, lots of visits to Boston.

**MS. KING:** Jim, was that for evaluation physically or was that for the informed consent process?

**MR. FINN:** Both.

**DR. KIELY:** Well, not to muddy the waters too much, since we're already on 2, we might as well just talk about this. Two of the issues that concern me around this relate to—I think we brought it up a little bit on the telephone, but not in great detail. Related to comprehension and ability to understand was the idea of mental disability and substituted judgment. I don't think we used the term substituted judgment in the phone conversation, but in looking at a lot of literature around informed consent, obviously when people become quite ill, family members or others make decisions for them. And I don't think we can go forward in this regard without saying, at least with our state of knowledge now, are we going to accept that in these cases? Are we going to take that off the table because of the many myriad issues we've brought up? And then again do we leave a trap door, if you will, so that this document, you know, will be flexible and be able to adapt a little bit to the future?

**DR. BLOOM:** Whatever you decide please remember that there are patients, for example, those who have had extracorporeal perfusion of their blood through liver assist devices, that are comatose, and they cannot make a decision. So you want to consider that in your judgment.

**DR. VANDERPOOL:** Well, as I mentioned about the Vatican's statement, the Vatican's statement says, "Okay. Should be all right to have patients receive experimental xenotransplantation on the basis of substituted judgment. " But that raises some real serious questions for me. I mean I wanted to describe the report and not begin to critique parts of it. But one of my concerns about that is it raises the questions related to death and dying when someone is in a comatose state, and you're not sure what this person would have really wanted. Didn't fill out a living will. Didn't talk to anyone. Doesn't have a durable power of attorney. And does the family at that point have the moral warrant to say, "Well, let's put dad on a respirator?" " I tend to think not. And so it seems to me that unless this person showed some desire for desperate heroic measures, in this case a xenotransplant, it would be very problematic to have a substituted judgment when that person never raised the issue. Seems to me that you'd have to have some documentation that the family was acting on behalf of what the patient would have wanted. Comments? I think both of them are critical issues.

**DR. KIELY:** It's critical. And that also begs the question, what about children?

**MS. SHAPIRO:** And what rules we have now, what laws there are now. And it's not very helpful in terms of the (indiscernible).

**DR. VANDERPOOL:** Robyn, please speak into the mic.

**MS. SHAPIRO:** The common rule simply says that a legally authorized representative can give consent to an incapable (indiscernible) without any definition. It says, "Look to your state law. " Well, a lot of state laws don't talk about research. I mean you may have healthcare participation, but for research participation most statutes have nothing about that, and they don't talk about levels of acceptable risk in research involving incapable participants, and they don't talk about the responsibilities of whoever it is who would make the decision. But if you can't do substituted judgment, then case law in other contexts would say then you go by best interests. So could someone argue? Let's say Jim was incapacitated at the time that he really needed this, and he'd live or he'd die. Well, could a surrogate research decision maker on his behalf say, "I think it's in his best interest to go forward because otherwise he's going to die?" " A court certainly would buy that. They don't want to come anywhere close to an option that would result in death

**DR. KIELY:** I can see the same circumstance with a mentally disabled adult or child or a child. And certainly parents would have the rights to enroll their child in a study and thereby commit them and everyone they know to a lifelong relationship with these researchers.

**MR. BERGER:** That would be fine under normal circumstances where they're the only ones at risk. But how can you take a child and put them into a lifelong monitoring system because you have no concept of whether they're going to be able to do that when it's a public health issue? For themselves you can do that, but not for everybody else.

**DR. BLOOM:** I'd just like to point out, being the person with the flies in all the ointment, that you've heard of different kinds of xenotransplantation. You heard—I think it was the first meeting—about patients that are being treated for cancer with their own lymphocytes that have been exposed to *Drosophila* fruit fly cells. Those may be children. They may have a child with cancer, and they may be treated that way. You will hear tomorrow—and I think Harold has heard previously—about a product that's produced by autologous, the patient's own cells being grown on mouse cells, and the indication there is severe burns. That may very often be children. And so when you make pronouncements about it's okay for children or it's not okay for children, please be aware of the different products and the different circumstances.

**MS. KING:** With what you were saying about substituted judgment, what if the situation never had presented itself? And I don't know the situation. But say there was an emergency. This has never been considered. The person never had a chance to think about, "This is something I would want or not want." And the family has to make a decision. I would venture to say that probably most people have not discussed what they would want with family members in any type of situation. Even those who have done advanced care planning typically haven't discussed it with their family, and most Americans haven't even done that. So I would argue that if we do say that, that we have to have some evidence that this is what the person would want. We would be really precluding many people from ever getting it. If we would do that, if that's what we want to do, then we can do that. But I think that we need to really consider. I think most people would never have discussed this.

**DR. VANDERPOOL:** So, for example, let's say someone was in a terrible car wreck, and both kidneys were destroyed, and they're rushed to the ER room. Well, of course, you could give that person dialysis and bring them back to consciousness. So kidney's all right. Maybe the heart were irrevocably damaged, and you did have the availability of an experimental pig's heart. You're saying, Karren, that it would be possible to have substituted judgment even if you had never talked about that? I mean I guess it would make sense.

**MS. KING:** Well, you couldn't use substituted judgment. You'd probably have to use, as you were saying, best interest. But I'm saying if we were to say that a third party, say a durable power of attorney for healthcare, whatever, the person appointed, say even legally or not legally, just the next of kin, if we're saying that they had to, in some way, have known what that person would want, because they are going to commit them to surveillance for life, I would say if we stick to that, we need to do that knowing that most people probably have never had those discussions. And so I don't think they could ever use substituted judgment typically with most people.

**MS. SHAPIRO:** I agree. I don't think that that would be the required standard. On the other hand, I think one could say that a surrogate can't, according to the best interest analysis, commit someone to this kind of procedure because of the risk-benefit ratio to the person, him or herself, not only lifelong surveillance, but what we heard this morning from Fishman about.

**DR. VANDERPOOL:** Of course, what we could do is say that our report is going to focus on the early phases, that at this point we can only deal with the sort of standard types of cases that are likely to occur in the early phases of experimentation, and we think that that level of early experimentation ought to involve competent adults.

**MS. KING:** To Eda's point, right now with the children with fruit flies and the cancer or whatever, that would say that those children couldn't receive that treatment, and I don't think we want to do that. I don't feel like I want to do that.

**MS. SHAPIRO:** Me neither. Where are we?

**MR. PHELPS:** Somewhere in number 2.

**MS. SHAPIRO:** Yeah, we didn't touch on a lot of these in 2. Who wants to talk about 2? Sharon?

**DR. KIELY:** I'll just start. This goes back to the researchers. The first thing we talked about, as listed here, about who should obtain the informed consent of the subject, while this seems like a pretty straightforward

issue, I'm not sure that it is. There seems to be, at least in our phone conversation, some concerns about the researcher certainly has the knowledge, the background, the expertise and what have you, but we kind of got stuck on the fact that maybe they might be approaching this at a different level that wouldn't be appropriate for individual patients certainly. And the issue that Karren and Brad brought up about sometimes these busy researchers don't really take the time. And I think in our phone conversation we brought up the idea that it would be more of a recommend more of a step-wise process with both researchers and educators available to the family and to the patient. And I think in AOPO and in different organ procurement organizations they have that type of a model. Do you want to speak a little bit to that, having somebody from the transplant community, you know, who has a standardized approach? And maybe there might be some way we could coordinate across those lines for this type of thing as, you know, we go beyond 200 INDs or whatever the number is now. Do you want to talk a little bit about that, their approach for education?

**DR. COLLINS:** Sure. Organ procurement organizations do it different ways, but I think the general model is that someone who's trusted, but who's not related at all to the transplant team, a trusted individual, they don't have to be a medical professional, they can be a chaplain or something like that, first addresses the family. And the studies have shown that those are the families that will consent more. Someone that is not related to the medical team and just comes in kind of as a third party and develops a relationship over that brief period of time as kind of a sounding board first and then brings up the organ transplantation as an option. I will say that I've thought a lot about this particular point, getting consent. We get consent certainly for operations. You're called. The patient is in preoperative holding. They don't have a consent. And you go up there and spend 30 seconds. It's terrible. I'm sure I could be sued hundreds of times for being guilty of this. But I've thought a lot about informed consent since we had our little phone conversation. But on the other hand, the person who's doing the research, you've kind of developed a relationship with them. That's part of the patient-doctor relationship, and that's what I like most about being a physician, that relationship that you have with your patients. I don't know where I fall on this particular point. I'm sorry. I've again confused the issue.

**DR. KIELY:** And from the recipient side—the donor side you just mentioned, but on the recipient side as well, we talked about they don't have a car. What education on the recipient side, and how are those folks sort of, I guess you could say, shepherded through the process?

**DR. COLLINS:** At Duke University they meet a lot of people when you seriously consider them for transplantation. They meet a nephrologist or a hepatologist who brings them into the system. They meet a social worker. And each of these persons is responsible for some education process. They meet transplant coordinators. They meet financial representatives. They meet the surgeon who may potentially do the procedure. Sometimes they even meet other patients who have had the procedure because we have groups that they can sit in on of post-transplant recipients. The education process, even before they're listed, is pretty lengthy. I don't think we do a good job, at least at our centers, determining whether the patient fully comprehends all that we're telling them, but certainly we give it a good effort to educate them. Karren, I don't know about your place.

**MS. KING:** I would agree with what you're saying. The dialysis kidney transplant is a unique group because there are federal mandates, and the federal government mandates, when someone begins dialysis, that they be told about all their treatment options, including transplantation. So I think there's a federal precedent that we do that. Again the depth of that or the comprehension of the patient is not really assessed, but I think the patients are educated, in the kidney transplant area anyway, with a wide multidisciplinary approach.

**DR. KIELY:** Jim, in your experience it took six months. Do you want to describe for the group a little bit about the many folks that you met along the way? Because I get the sense that while you still had no problems with going ahead and signing the document, while you hadn't read the whole thing through and through, as you pointed out, it seems that you did have a sense of some of what you were up against, certainly from your personal perspective, but you also had a good sense too about what was down the line, although you said you read the detail later.

**MR. FINN:** I signed on the line and read the contract after I signed basically.

**DR. KIELY:** You said you knew what you needed to know. So do you want to go through your six-month

process a little bit?

**MR. FINN:** Well, I knew it was going to be an experimental procedure. No promises were made whatsoever. In fact, I was told there was a good possibility I would not achieve any good results. They're very cautious. This is phase 1 of Diacrin. This is the first show of it basically. They explained carefully my options for my situation, which were none. There were no other options. Medication does no longer function for me. So they didn't back me into a wall. I'm not trying to imply that they ever did. I put myself against the wall. I knew what I was getting into. It was very carefully explained. I didn't read all the details until after I'd signed because it made no difference to me at that point. No promises were made. I was asked to volunteer as a potential good could come out of it, but if not good for me, then good for other people who would come after me. So there was some of that to think about.

I don't know what else I can say really. It was a very involved procedure. I'll say that much. It involved lots of neuropsych work, lots of blood work, endless PET scans and MRIs and CAT scans. I met with the surgeon before it was done. He explained what he would do. It was mapped out very well for me. And in six months you have enough time to get a feeling of what's going to happen. It's not like I rushed into this. I had the time to back out if I wanted to. I didn't want to.

**MS. KING:** Jim, did you have other people, like the third party kind of consent, that were involved in this process at all, or educated, others in your family, close friends?

**MR. FINN:** A close friend saw me through all of this. There wasn't much in the line of education for him. In fact, my form, as you see it in the book, my form even has an out clause. I could quit any time I wanted to. I think they've changed that. But that was phase 1, and that wasn't covered.

**DR. VANDERPOOL:** Now, who is "they," Jim? Is "they" the physicians or is "they" a significant number of other people?

**MR. FINN:** "They" would be my doctor. I even saw one doctor at Boston University. I had a 10 or 12-year relationship with him. And he could no longer do anything for me. And he turned me over to his partner, who was involved with this research project with Diacrin. And they opened the door to me and said, "If you want in, you're welcome."

**DR. VANDERPOOL:** Now, your experience is something that, at least in the past, is very friendly to me. Let me just put the alternatives in a little starker form. Who should obtain informed consent from prospective subjects? I argued in my Lancet article—didn't argue strongly, but just basically said that I thought informed consent should primarily be the work of the healthcare team because I thought the relationships needed to be rich and meaningful between the healthcare team and the patients. And if you have a patient advocate who does the consenting, and then the physicians come in and do the work, that means the physicians are primarily, you know, the technical experts. But they don't really tie in with the patients. They're not even expected to. In fact, by having someone else do the consenting process, the physicians are rendered sort of outside the loop of this very maybe most important decision the prospective subject will ever make.

Now, over against that argument that I made in Lancet, the Nuffield Council in UK says, "Hey, you've got to have someone besides the physicians doing this." And I think what the Nuffield Council is working off is what the Institute of Medicine Report in 1996 talks about, which is if you look at the history of xenotransplantation, it's a history of overselling by overly zealous physicians.

**MR. FINN:** Baby Faye it says.

**DR. VANDERPOOL:** That's right. And they're working off Baby Faye. You know, they virtually promised the parents she'd end up in college instead of dying, what, four weeks or something, or that possibility. And then everyone who did one of these from Starzl to Reemtsma were very excited about, "Hey, we've got this full-proof message now." "Not full-proof, but they were very enthusiastic and committed to what they were doing. And so that's the IOM view is look at the history and look at the degree to which physician researchers can be overly optimistic about outcomes. So they're going to, without any ill-grounded attempts, be more

optimistic, more upbeat, and so on, and it's going to take someone outside of that team to really tell it straight, give the benefits and doubts and so on. And David Cooper and Paul Lanza, who wrote the book on xeno, more or less agree with that perspective. Cooper's a transplant surgeon, and he's saying, "Well, look, it would be better if consent were obtained by someone else other than the surgeons. " So I'm intentionally presenting this as a contrast because I think we need to discuss this and see what we think. I mean maybe we could say both. Are we going to go with the nonphysician advocate or are we going to go with the physician team? That's a big decision for us to try to make.

**MR. FINN:** Why can't we have both?

**DR. COLLINS:** Yeah, I agree with Jim. There may need to be some compromise that would involve both because, as Sharon can tell you, when you have to consent a patient for something, and you have a good relationship with them, you can sell them anything. I agree that perhaps both, the persons involved in the study, as well as an independent party.

**MR. PHELPS:** Not a choice between two, but both avenues at the same time.

**MR. FINN:** That's what I mean.

**MR. PHELPS:** Right.

**DR. COLLINS:** Right.

**MR. BERGER:** Yeah. I mean why don't you just have something on that form that an independent third party patient advocate has to sign off on the form that they've had the opportunity to discuss with the patient the informed consent form, just a sign-off, because I tend to agree that the medical team in these cases over a long period of time should establish some kind of relationship and will probably be the right person, but I would agree that someone else has to come in there to make sure the patient has every opportunity to ask whatever it is and get whatever other information and assistance.

**MR. FINN:** I suggested that Diacrin hire me, as a matter of fact. I went to them with my proposal about four years ago. They didn't shoot it down, but I'm not working for them either.

**MR. BERGER:** That's probably a financial conflict of interest.

**DR. VANDERPOOL:** But I think, Alan, knowing you, you probably have more packed into your statements than just that I heard. What you're not saying is the physicians who have a real ongoing relationship and talk to the patient and the patient definitely decides to go ahead, at that point the patient advocate comes in and says, "Hey, you know, my name is so-and-so and so-and-so. I'm not an M.D., but I'm here to make sure you know what you're doing. " I mean we wouldn't use that phrase. Well, it seems to me that you may as well just go with the physicians on that model. So some way or another the patient advocate person has to have a real meaningful, trusting relationship also, and in order for the patient to say, "Look, I hear you, and I hear the physicians, " maybe we'd want to recommend that the third party would go first and talk to the patient and begin the process of information and counsel and let them know, "Hey, this is your choice. Don't feel any pressure from anyone other than what you and your family think is best and so on, " at which point the physician would come in. I don't know.

**MR. BERGER:** Yeah. I don't know how. Yes, there would have to be some relationship. Maybe it's a simple statement that we devise that that third party has to sign off that they have had adequate time, however you want to state it, so that we don't put some rule, it's got to be three meetings or whatever, but that they just have to sign off on, just a simple paragraph, that they've had adequate time to talk with the patient over all their options and feel that the patient has had adequate information to make their decision. I don't know whether that's a legal problem if someone says that.

**DR. KIELY:** I have a question. All I was going to say is that I think we're focused, and maybe it's just the way I'm reading this on the point of this signature on this informed consent, that this is really a process, and yet,

largely much of what we're talking about is who gets the consent, which is so different, because that's why we went through this with Jim about six months of learning about the procedures, understanding who's on the team. He talked about the fact that the relationship with his physician of 12 years was disrupted because the physician could do nothing for him. And then he was transferred to the care of the researcher.

So we are talking about something that just is a little bit different than renal transplants and others, although we can learn about what happened in those spheres. So my point is I don't want us to get so focused on the piece of paper, although it's important, because we talked about, in the phone conversation, the process, and that the procedural issues might be—we might be better to spend more of our time going over what are the necessary components or processes that should occur as opposed to what this signature on the piece of paper means. It's a very different thing than when I do a procedure in my office and usually get the consent after it's done. I mean, "Oh, we forgot to get the consent because the patient just wants their skin tags removed. " Anyway, don't count that.

**MR. BERGER:** This was a public comment.

**DR. KIELY:** But the point about this is it does happen, and I think Brad's been very up front about the fact that there's a lot of flaws in the system as it currently exists. But the thing that we're faced with in this discussion, as you brought up several times, Alan—and it's very true—is that our feet are held to the fire on the fact of the public health implications, and they're unknowable at this point. I think we talked about the unique aspects. While I think we realize in any medical research there are going to be unknown complications, unknown effects, it may work, it may not, as simple as that, you can't even guarantee it will work. But when we get down to this process, the unknowns will be discovered years in the future. So that's a very different piece.

**MS. SHAPIRO:** I think you're right. I think that the challenge for us is to go back and look at what we're trying to accomplish in the process, and there are two things that I think are accomplished by both potential players. One is to be sure that the information is disclosed. And I don't see how that can be done better than by the person who's going to do the operation. I think that has to be near the first part of the process.

And the second part or the second goal of the whole informed consent process is to assure voluntariness and understanding. So why can't you have a conversation, not get a consent, certainly not have a signed form, don't even have ask for an answer, have a discussion, you, with your patient, about what this would involve, have some other patient advocate kind of person go in and say, "What can I do for you? Do you get it? Do you want me to help you ask more questions? Do you want me to give you an out? " Kind of like the donor advocate for living livers. You know, the literature suggests there should be some donor advocate who can have veto power, can kind of put a halt to the process without the incredible enthusiasm of the team to go forward. So I mean I think that there are a few conversations here before we get to the signature on the form, but looking behind the purposes of informed consent globally.

**DR. VANDERPOOL:** That's really good. I only have one proviso, Robyn, to what you said. And that is I do think the person who talks about the benefits and risks and immunosuppression and possibilities of rejection and all of those needs to be the M.D.s.

**MS. SHAPIRO:** Absolutely.

**DR. VANDERPOOL:** At the same time I think the person who probably may well do better or best with the infectious disease risk could be someone other than the M.D. because at that point this person could be very knowledgeable about the public health implications and say, "Okay, you've talked to your physicians about the harms and benefits. How do you feel about that? " And as you say, I think I really like the word conversation. "How do you feel about that? " And scope that out.

There's another side to this that we need to really talk about, and I want to get your views about this, and that is that there are—and then you start talking about public disease risk, and therefore, certain things follow from this, and these include, and then go through the Public Health Service information guidelines where lifelong monitoring is required and regular checkups and autopsy. You know, this could be something you wouldn't want to do. It's going to take some time. What do you think about this? And so it might be best to have both

and have the physicians deal with the harms and benefits side and the non-physicians deal with other dimensions. We may be beginning to reach a consensus on some of this. I'm not sure.

**MS. KING:** I agree with what both of you are saying. I do think there is a precedent already in the transplant community where that kind of thing is already done with the team that sees the potential patient. But I also want to stress, Sharon, and the point I was going to make earlier you also made. I think earlier we were almost assuming that the patient has a trust relationship with one of these people already, like their physician. I think typically it's probably not going to be anyone they know at all. I think it's like what Jim was saying. Whoever they were seeing and treating them is probably not at all going to be the xenotransplantation individuals. So I think we need to make sure we clarify. We're talking about a relationship of trust, and I don't think that's going to probably exist with that xeno team unless I'm totally missing how it would seem to function.

**MR. FINN:** It existed for me because of the uniqueness of the program.

**MS. KING:** But in many cases they're probably not going to be in the same town as the people maybe doing the research. I mean I think it may be a totally new group of people. So I think we want to put aside the idea that someone who they trust should maybe be involved in it because I think that's probably not going to be an option for most folks.

**DR. VANDERPOOL:** Would you, Karren, still be in favor of the physicians handling one side, that even though they're new, they'd have to get to know the patient?

**MS. KING:** Yes.

**DR. VANDERPOOL:** They'd have to establish a relationship?

**MS. KING:** I think that's often true, again, with transplantation. I think the kidney transplant surgeon, physician is also—we're talking about the xenotransplant researcher is very gung-ho on this procedure. I think that's probably true too for the transplant surgeons. And they're going to present that side of it, but the other people that see the individual present other sides of it as well. Not that the surgeon does. They do. But they're probably the most person selling just like the xeno researcher is going to be. They really believe in what they're doing versus other folks, for example, with dialysis, they see people that don't get so successful with it. So I think that that model exists, and I feel very comfortable with that. And in many cases the transplant team doesn't know the potential patient with allografts either.

**MS. SHAPIRO:** Well, we kind of talked about A. How about B? Anybody in this little working group have anything to say about comprehensibility of the informed consent document? We've talked around it, but we got kind of specific in our meeting I guess. How does the length of the form and the patient's mental and physical health affect comprehension? How much time is allowed/devoted to reading and signing the form? For whose benefit are the forms so long? If you edit them, what do you cut out? We've talked about some of this.

**MS. KING:** I think the eighth grade reading level was suggested for some. When you look at the terminology in these things, that's difficult. I was interested in looking at what we were given to read looking at there's two different types of informed consent, one like Jim's that actually details everything within that form. The other basically would say, "These things have been discussed," but that's not all part of the consent form, and indeed, that's done in another mechanism. Legally what do you think about the two different types?

**MS. SHAPIRO:** There's one purpose of a document et al. We've said now four times here this afternoon that the legal requirement is the process. The legal and the ethical requirement is the process, and the documentation is proof that you went through the process. So if you're more explicit on the one hand, you can say, "See, they signed, this is it." "On the other hand, the patient could come, especially if it's at a hundredth grade reading level instead of eighth, "I didn't understand that." "So maybe you're better off with something that says, "This was explained," and then whoever did the explaining is a witness, and they get up there, and they say, "This is what I explained."

**MS. KING:** And they have a record of what was presented. Like they have an outline of things they are to talk

about or whatever.

**MS. SHAPIRO:** Something in the progress notes. Something, yeah.

**DR. CRONE:** I think what you're risking is—you know, I saw that about oral report, and I think, given the fact that xeno is going to be so scrutinized, I think you'd really have to think twice about, you know, a form that says, "Oh, yeah, you talked about it, it was presented," because you really are going to want to make sure that it was very well covered.

**MS. SHAPIRO:** But still what you could do is to have the consent form itself say, "I talked about everything that was important," and then on another piece of paper detail what it is that you talked about instead of making the patient hold on to that.

**MS. KING:** That's what I envisioned. It could still say what we discussed, but it wouldn't go into the detail. It would be more the headings of what we discussed. But I know what you're saying.

**DR. KAISER:** I'd just like to read from the regulations here. I guess it's the 50.25 regs. This is Title 21. It says that the basic elements of informed consent, quote, a statement that the study involves research, an explanation of the purposes of the research, and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental. So that's in the regs.

**MS. SHAPIRO:** But it doesn't say how detailed a description.

**DR. KAISER:** It does rule out saying, "We've discussed these all in another piece of paper."

**MS. SHAPIRO:** No, I don't think anybody was really suggesting that.

**DR. CRONE:** I think that the common goal for the CFR, it does give you those two options, but I think those options are missing from the FDA rules. I think that's the discrepancy.

**DR. VANDERPOOL:** I think that's a good point. The CFR 46.107 talks about primarily in terms of the information that needs to be presented. It has a little paragraph on comprehension and non-coercion or undue influence. I think it has one sentence on that. Then it goes to the information that has to be told. And so it's no wonder that IRB spent almost all their time on what the information is and whether it's sufficient. The question of having true conversations and securing understanding and true voluntarism is really not a focus in the federal regs. It needs to be. And I've actually presented a paper for the National Advisory Commission to the effect that the CFR needs to be retooled to reflect Belmont's three emphases.

Let me ask this question about the possibility of our having some consensus. We pretty much agree that physicians need to talk about immunosuppression and so on, namely, the harms and benefits, risks and benefits, the non-physician about public health risk, lifelong surveillance, and so on. This would take care of most of what's in the PHS guidelines. And each discloses essential information, assures comprehension, secures voluntarism, "yes" or "no" or "I'll wait a while" or whatever. Are we pretty much agreed on that? If the physicians talk about these things and the non-physician about these things, and the consent form has a sign-off on both of them, then we certainly would want to say, in the light of what informed consent is, that the essential information has been disclosed, there's been adequate comprehension of it, and voluntary consent has been given.

**MR. BERGER:** There's one more point that's coming up later because I do think it's more important here, and there are probably some good examples that people can address. But there's a financial conflict of interest that needs to be discussed, I believe at the front end, because many of these cases are going to be one where there's dramatic financial interest in it because you have companies with products that are going out on the market where people have stock and stock options and so forth. And I'm sure there are good examples with artificial organs and other products, but it seems to me that has to be addressed at the front end. I know it comes up later in this outline, but that should be part of the process and at the earliest stages.

**DR. VANDERPOOL:** Alan, just because companies are going to make money off of this operation doesn't mean that a researcher has to disclose that fact, but the researcher would have to disclose that he or she has a thousand shares in the company the organ is coming from or something like that. But I think those sort of egregious conflicts of interest are going to be by and large avoided.

**MR. BERGER:** I'm not sure how they would ever be avoided. The comment that we heard earlier from the attorney representing Health and Human Services is to avoid appearances of conflict of interest. I mean I believe that very strongly. So I think there will be dramatic financial interest in this that should be disclosed. I don't think someone has to say, "Well, we could earn \$10 billion if this happens," but that should be really at the front end so the patient is quite aware, when they're hearing what this team is telling them, that they do have a strong financial interest in the outcome. That may not change someone's opinion, but I certainly think that that has to be known.

**DR. BLOOM:** I, not being part of this working group, but would second that. I'd give as one example where there was an appearance that ended in disaster as the Jessie Gelsinger case.

**MS. SHAPIRO:** But we do have an outline on that too on financial conflicts of interest with what's out there now and what recommendations we might consider. Right now human subjects don't have to be told about this stuff, and I think that we should for our own recommendations adopt that for significant financial conflicts of interest.

**MS. KING:** I go back to what you were saying about each of these parties has to assure comprehension. Are we going to talk more at some point about what that would mean?

**DR. VANDERPOOL:** We need to address that too.

**MS. KING:** Okay.

**DR. VANDERPOOL:** In fact, we need to talk about lifelong follow-up, the form that has so many complexities and so much detail, about the length of the form, worries over confidentiality, yet I think we need to talk about what it means to assure comprehension. Absolutely.

**DR. CRONE:** In regards to those people, like some of the patients who have Parkinson's disease, will have had problems with, you know, where they had cognitive impairment, or we see people with organ failure all the time who have cognitive impairment. So that's going to definitely have to be beyond the issue of just their education and their ability to understand. Just as a step back to play a devil's advocate on something, you know, I feel very strongly that the physician has to provide the information because that's part of the relationship, the patient-physician relationship, is to be able to sit down and tell them about what they're going to be facing, these are the risks, these are the benefits. When I look there and we say non-physicians can talk about the public health risk, lifelong surveillance, et cetera, does that remove the physician a little too much from his or her own realization about the implications of what they're doing about the procedure?

**DR. VANDERPOOL:** That's a good point. Lilly, good to have you here. We talked earlier about one thing you just mentioned over how if the physicians aren't part of the informed consent process, that kind of relationship that ought to be there will just simply not be there as the way it should be. I'm not sure that the physicians not doing the consenting with the infectious disease issues would mean that they wouldn't think about them or take them seriously or not. What does the rest of the group think about that? Are you thinking that this sort of gets them off the hook about worrying about it?

**DR. CRONE:** I'm just concerned also about the financial issue because this is kind of going to be an unusual situation with xenotransplant is that a lot of them I think are going to come from people—there's going to be more corporations sort of with people with real financial interest, so it's going to come from a very different background than other typical types, allotransplantation, where there clearly isn't quite the same financial interest in the sense of it's something that could be this big investment and have all these shares. I mean typically people who do it, the surgeons who do it, don't have a lot of shares in the medical center. They may

want them, but they don't. And I guess that's part of when Alan brings that up, it makes me think about jeez, you know, and maybe it's sort of a paranoid way of looking at it, but I'm just concerned that the people who are going to do this are going to be held up for the full degree of responsibility, and sometimes I think that there are other things that can kind of sway them.

**DR. VANDERPOOL:** Well, maybe we need to hash this out more, but I'm not yet convinced that all financial interest needs to be disclosed. It seems to me that there are instances when they would have to be, and there are other things that why should it matter. You know, every other protocol that IRB gets is drug sponsored. We're not doing it, but maybe we should be telling the patients that this is being sponsored by such and such a company that stands to make a significant amount of money if you and others are experimental subjects and the drug ends up proving to be a good drug. My question about that is, isn't the real issue whether the drug is going to work or not compared to standard drugs, and the patient is primarily concerned about what he or she stands to benefit or lose by this, and unless the researcher has a level of financial interest that would color that person's thinking, then should it be entered on a consent form? Argue me down.

**MS. SHAPIRO:** On page 1 of the outline on this there are the federal requirements for financial disclosure, which isn't the universe, Harold, but which is significant financial arrangements.

**MR. PHELPS:** Which page 1 are we looking at?

**MS. SHAPIRO:** The outline is Special Problems/ Questions - Researchers' Financial Conflicts of Interest. It's a three-page outline. And Roman numeral III talks about what has to be disclosed. Why shouldn't that have to also be disclosed to the human subjects? That limits it to those that may have an impact. It starts at the bottom, and then it goes to the top of page 2.

**DR. RUSSOW:** I'd like to back up a bit. I think these are all very important questions, but just to get clear on this agreement about physicians and non-physicians and what their special requirements or duties are, I think that in one way or the other it may be the non-physician needs to say a lot about quality of life. The patient needs to be informed about the obvious having to go through a lifelong surveillance and so on, but also what kind of quality of life can he or she expect in terms of both medical conditions, and equally important, social conditions, you know, things like—we've mentioned specific instances of it—like breaches of confidentiality. But I think we need to be thinking more broadly about assuming that the patient lives, how will the quality of life be for that person.

The other thing I would want to add is sort of going back, to some extent, to the information that's required is kind of patient driven. The patient has to decide, "I don't want to read anymore, I've got the idea," or "I want to, for example, consult with an expert on Catholic theology or the Judaic tradition or the Islamic tradition before I make that because my religion is very important to me." They ought to be afforded that opportunity, and that sort of, I think, goes more to the category of the social implications of quality of life. Take an extreme example, which we know is not true. Suppose the Catholic Church said that "you will be excommunicated if you have this done." That's an important thing for the person to know if he's a Catholic and cares about these things. So I would just say that somewhere in there we'd have to make sure that we don't lose sight of all the dimensions of quality of life.

**MS. KING:** Lilly, I agree strongly that quality of life is an important factor. My concern is we don't know at this point what quality of life would be with xenotransplantation. We know some things from the literature with allografts, but we really don't know, and it's really speculative at this time. The other thing I think we have to be real careful with as clinicians and looking at quality of life issues is that we are not able to assess anyone else's quality of life. So we need to make sure that we don't impose our own view on whoever this person may be about quality of life on another. Again as we have more xenotransplants, we will be able to know that. One of the articles did suggest that one of the things that would be encouraged in looking at xenotransplantation is that the researchers not only look at things like mortality, morbidity issues, but also to look at quality of life of those. Jim, I'm curious. Is that something that's been looked at with your studies at all?

**MR. FINN:** In my case it was the overriding decision. You don't generally die from Parkinson's disease.

**MS. KING:** But once the procedure was done, has the study continued to work with individuals like yourself who have gotten the procedure to look at your quality of life issues?

**MR. FINN:** Yes, quality of life, plus medical issues. And it's ongoing. I'm five years out from the operation now. I celebrated my fifth birthday a month and a half ago.

**MS. KING:** Great. But I do think that's beyond the purview of informed consent to say that we would encourage, but I would hope our group as a whole might take a look at that as something that we would like to encourage the researchers to look at as well because it is much broader than just physically they're still living, which is important. But how is their quality of life as they perceive it? But I don't know at this point—and we could say, I mean we could ask that in the informed consent process that this be discussed, but that at this point we really don't have—it could definitely impact negatively, it could impact positively. We really don't know.

**MR. FINN:** Living was not as important as the quality of life to me.

**DR. VANDERPOOL:** I very much agree with you, Lilly, on the need to accent issues of quality of life, however we could use that phrase obviously, but primarily this would press researchers to think about the probable way of living this person will have. I mean are you going to lie in the hospital and be on tubes and immunosuppression that you'll get a cold from every cold germ that comes along, all kinds of opportunistic infections? What will life probably look like for you? And this accent is found most strongly, other than how Lilly voiced it, in the Nuffield Council Report. It really emphasizes the, quote, robust, closed quote, need to describe issues related to the quality of life, and that's just more or less a common-sensical description of what the health team foresees in terms of what will happen medically and when you'll be able to leave the hospital and things like that. Now, you may not know very much to be able to say. In that case you'd probably need to say that "we don't know a lot about it. You could experience this or you could experience that, " but at least let the persons envision what their life would be like post-transplant.

**DR. KIELY:** I think we touch on a lot of things that have to be part of the informed consent. The surveillance is a quality of life issue technically. Everything relates to the fact that "we don't know if it's, " like you pointed out, Jim, "that it may work, it may not. We can't tell you. " So I have some concerns about actually putting the terms quality of life per se. I would have a hard time qualifying that. But I think we can speak to issues, the requirements, if you will, according to our guidelines and what's required by law that may impact quality of life, but that's the only way I could see including that.

**DR. RUSSOW:** Yeah, I agree with what you said. I guess my concern was more that if the research team and the physicians are the main people who supply that information, they're likely to concentrate on the medical end of things. What will it be like for you in terms of your physical health or what might happen? But I was trying to emphasize that quality of life for most people is not exclusively a concern about what the state of their medical health is, but it might involve other things as well, more in terms of their social values and their other value system that may say, "Look, it's better to die than to do X. "Now, not a lot of people would think that, but everybody, I think, would have something they'd say that about. And so we need to be sensitive to the fact that quality of life is not determined solely by the state of the patient's physical health.

**DR. CRONE:** But if it goes in the direction of a lot of transplantation research, transplant studies they do now, that there is, though, already a lot of quality of life, there is a tendency to focus on that even as new technology comes out or new procedures, like living donor, because there's still a lot of sort of questions we don't have long-term. So the precedent has sort of already been set in regards to transplantation, which is a positive, you know, that there is some of that within the transplant community, that there's questions of quality of life that seem to be built in that is not necessarily built in in some other procedures.

**DR. KIELY:** But insofar as informed consent is concerned, while the research protocol may call for ongoing evaluation or qualification, quantification of quality of life indicators, that's a separate issue than including an issue of quality of life in the informed consent. And again issues of sexual contacts, blood tests, how many PET scans you have to have, requirements for all the reporting things we're talking about here, they will impact quality of life, and in fact, may be the deal breaker for a certain patient who says, "Well, I can't live like that. I'm not going to subject myself and my wife or whatever else. " So I think insofar that is concerned, but my

other statement stands.

**DR. VANDERPOOL:** By the way, our next session starts in about five minutes, so don't we need to break? We've got a beautiful start here. We're on a roll.

**DR. KIELY:** It's really hard to break up now.

**MR. PHELPS:** One clarification, if I can get it.

**DR. VANDERPOOL:** There's another open-ended question. We need to figure out how much we need to meet and how much we can handle over e-mail and so on.

**MR. PHELPS:** We'll get some of this down on paper, get it circulated. You'll be able to have another teleconference, if you need one, to decide what to do next. There are pieces of this that didn't get a chance to get brought forward. I want to ask one question. Does this person have to be a non-physician? Couldn't that be a good, sensitive epidemiologist?

**DR. VANDERPOOL:** Or family physician.

**MR. PHELPS:** Or family physician.

**MS. SHAPIRO:** Or anything.

**MS. KING:** A physician that's not directly involved with the procedure, correct?

**MR. PHELPS:** I just don't want any more mandatory jobs for counselors.

**DR. VANDERPOOL:** Good. It's a non-team member.

**MR. PHELPS:** Non-team member.

**MS. KING:** I don't know if you want to say a non-team member because the team member may be the nurse and social worker and other folks that work with these people once this is done.

**DR. VANDERPOOL:** Non-surgeon? Are we going to jump on Brad?

**MS. KING:** Maybe.

**DR. COLLINS:** That's all right.

**DR. CRONE:** But I agree with Karren because I think what she's saying is that it may not have to be—it may be a team member because I know in our center that's a team member. I mean the patients will hear education by several people, by the physicians, by the social worker, by the nurses. And certainly sometimes the nurses can be—

**MR. PHELPS:** All part of the team.

**DR. CRONE:** Yeah. I mean I like the fact that things are reiterated.

**MS. SHAPIRO:** Non-surgeon I think is what it is.

**MS. KING:** Maybe the physician not involved with the procedure.

**DR. VANDERPOOL:** Maybe a transplant surgeon. We'll have to talk about them over time. We haven't really dealt with the length of the form. Seems to me the length of the form could be a lot shorter if you're just talking about informed consent, but the institutions and the companies are going to call for a lot of very lengthy

forms to make sure what the legal liability issues are, and that's something we need to try to crack.

**DR. CRONE:** One of the things was the consent form that was here in the packet. And reading that, it's probably one of the most clearly written consent forms I've seen in the sense that it was written, and it's lengthy, but it is understandable, which I mean I think more my concern is understandability because I have definitely seen consent forms that are a little shorter, but either they're jam-packed, and the way they're jam-packed is like they're overwhelming, and you can't process it.

**DR. COLLINS:** Expanding on that point of understandability, one issue, I guess, different language, Spanish-speaking patients, for instance, and also folks who are illiterate. I guess they would have a family member sign for them, but how do we test their comprehension of what we're telling them?

**MS. KING:** And even, Cathy, what you were saying, I think it was clearly written, but the educational level that it would require to read that. It was clear to like you or someone around this table, but I think for a lot of folks, the terms that they would use, it's hard to break those terms down. I think the readability level would have probably been a college level.

**DR. CRONE:** I don't know. But I just thought even then, though, that to me it was probably more easily readable than I've seen before. I mean someone did a lot of work for that. And at least they explained some of the different terms, which is really nicely done.

**DR. VANDERPOOL:** Shall we break? We're supposed to start really soon. Cathy, I'm sorry I called you Lilly a while ago. I thought you were going to be here tomorrow, and here you are. Thanks so much for coming all the way from Pennsylvania, right? It's great to have you.

**MR. BERGER:** Robyn, one question. Do we have or can we get an actual legal opinion as to whether the surveillance can be made mandatory? I've never seen anything.

**MS. SHAPIRO:** I don't think it can without some kind of exception because if we go to that outline, the part of the law that poses us a problem is lifelong surveillance, 45 CFR (indiscernible), elements of (indiscernible).

**DR. VANDERPOOL:** She's waving. Can you speak into the mic, Robyn?

**MS. SHAPIRO:** The following information shall be provided to each subject, 8, a statement that participation is voluntary, the refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

**MR. BERGER:** So we're saying that it would be illegal to have a patient sign a document that they would have to do lifelong mandatory surveillance?

**MS. SHAPIRO:** I mean I don't represent the government, but I think that we could write a document that would say "part of this protocol is lifelong surveillance" and not go any further than that. That is to say "and if you don't do it, you're going to go to jail" or anything like that because that really couldn't happen. Now, what might happen, given the nature and severity of the risk in terms of the public health response, is something else. Am I out of line? Couldn't you write a document saying, "part of the study is lifelong surveillance, " written like that?

**MS. SHERMAN:** She's looking at me because I work with the General Counsel's Office in the Office of Human Research.

**MS. SHAPIRO:** This is Susan Sherman.

**MS. SHERMAN:** I think you could. I'm not sure that would pass muster with OHRP, but you have to remember the regulations you're looking at are only going to apply to generally-funded projects, so there is that limitation (indiscernible) also that type of research. The other option is a waiver provision within the

regulations. The department head can waive particular provisions.

**MS. SHAPIRO:** And maybe part of what we should do is to consider whether we feel strongly enough about this that we would want to go and ask for a waiver because of the special circumstances about this kind of a research protocol.

**MR. BERGER:** The surveillance protocol is based on the fact that you're going to do lifelong monitoring. So if you can't do it and you can't enforce it, then we don't have a security system for public health, which makes this a huge problem.

**MS. SHAPIRO:** So maybe what we do in this paper is to recommend that we get some kind of waiver.

**DR. CRONE:** I also wanted to add to that though. That doesn't address the enforcement issue. You still have the enforcement issues, and the quarantine laws, I think, are state-based.

**MS. SHAPIRO:** But this would let us not include the part that says you can withdraw at any time.

**DR. BLOOM:** I'd like to say that maybe the OHRP regs just apply to federally funded, but FDA regs apply to everything, and our regs also have that right to withdraw. So you should look at those too.

**DR. VANDERPOOL:** All right. Let's get back to the group. Thank you all for coming.  
(Whereupon, working group session ended at 4:20 P.M.)