GENETICS SUBCOMMITTEE
NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

DR. MURRAY: Let us call this meeting to order. Good morning. This is the 9 December meeting of the Genetics Subcommittee of the National Bioethics Advisory Commission. I want to welcome all members of the commission, commission staff and guests.

We have got a lot of work to do today and we have a few people here who we have requested to be here in order to help us with one issue or another but, as I understand it, we have no formal scheduled appearances by guests.

If anyone wishes to speak during the time offered for public commentary and testimony, please indicate that wish to a member of the commission staff--I guess Pat--to Patricia Norris, who is standing in the back there. Otherwise, I think we should dig right in and try to make progress today.

Today is an opportunity for commissioners to talk amongst themselves; to try to reach agreement, insofar as possible, on the substance of the report. You have, in your handouts, a proposed tentative outline of the report and the various chapters.

We would like, by the end of the day, to know the areas--points--on which we have substantial agreement.

We would like to have some characterization of that agreement that we can render into a text.

We would also like to know what holes there are. That is a very important part of our task today. If there are specific things that ought to be in the final report--descriptions, analyses, et cetera--that we haven't yet commissioned, we need to know what they are, and we need to have at least a beginning of a plan on how we are going to fill those holes. And we need to know what areas of substantial--

MS. HYATT-KNORR: This was at the--

DR. MURRAY: We need to know what areas of substantial disagreement remain.

We have this tentative outline. At the end of the meeting, we will revise the outline and circulate it back to ourselves, of course, but also to the other members of the commission. We would like for them to have some idea of what we are going to do.

One other imperative that we have, which we won't try to accomplish today but rather set out today, is which other groups, individuals, et cetera, ought to be responding to the report, giving us feedback about its nature and substance, and we would like some-- We may solicit your help in figuring out who those people and

groups are.

That is all I have by way of introduction.

Henrietta, is there anything else administrative that you need to say?

MS. HYATT-KNORR: Well, those of you who seem to be concerned about the cost of the room, that is what we agreed upon, and certainly we are prepared to reimburse you, so just don't worry. Be happy. That is it.

DR. MURRAY: Okay. Very good.

DISCUSSION OF PREVIOUSLY COLLECTED TISSUE SAMPLES

COMMISSION MEMBERS

DR. MURRAY: Let us jump right into the first item on the agenda, which is--

The agenda today is basically just in three big chunks, except for the public statements. The first chunk is previously collected samples, the second chunk is community consultation, and Bernie, I hope, is going to lead us through that, and the third is tissue samples collected after whatever the effective date is of our recommendations.

And we have a sample of the work that has been done by the National Action Plan on Breast Cancer that we can look to for that. At least one member of that project--Debbie Saslow(?)--is going to be joining us for

that conversation.

So let us begin with previously collected tissue samples. Does anybody wish to start?

(No response.)

DR. MURRAY: Do we know where we are on this?

Zeke, would it be helpful to put your--

DR. EMANUEL: Do you want me to put up the old--

DR. MURRAY: --plan up on this?

DR. EMANUEL: --framework?

DR. MURRAY: Sure.

DR. EMANUEL: This is just a framework. And I think one question is whether that framework still holds or whether we want to re-think it. And I think I have the recommendations for the proposals I had.

I guess one question is whether that--those boxes--still makes sense to people, having thought about them now for about a month and a half.

REPORTER: Excuse me. Could you use your microphone.

DR. EMANUEL: Sorry.

DR. MIIKE: Zeke, the bottom two, when we get to community consent--

DR. EMANUEL: Right.

DR. MIIKE: --what is the difference operationally between community consent "full" and community consent presumably with "opt out?" How does a community opt out?

DR. EMANUEL: Well, they raise objections I think, as opposed to-- I mean, one is putting the onus on the researcher; one is putting the onus on people out in the community who want to object, I think. That is the way I imagine it.

One is we do something to inform people what we are up to. We distribute a letter, we contact organizations relevant, and we wait for them to respond.

The other is we actually, as researchers, go to them and solicit their advice, but we don't go-- We aren't permitted to go ahead unless we have some sign-off that we think is a sign-off.

So I think one, you know, it is a measure of who has got responsibility and where the responsibility for raising the concerns lies. It is also a measure of how much I think leg-work, effort, for really getting the community, or community leaders to sign off on it.

MS. KRAMER: But, Zeke, we haven't-- We didn't really discuss all of that.

DR. EMANUEL: No. No. I was suggesting

initially just are the boxes around, and then we can talk about the content inside. These are my ideas.

MS. KRAMER: Right.

DR. EMANUEL: And they are all tentative and they are not to be suggested for the commission. If you want me to put up the other one, with the blank boxes, I am happy to do that.

MS. KRAMER: No, no, no. I just-- I just wanted to make that point because I think Larry missed the meeting at which we initially began going through the boxes. You were a voice.

DR. MIIKE: No. The next question I was going to ask was that I assume we are going to--Bernie is going to--lead the discussion about community consent.

DR. LO: The next section?

DR. MIIKE: Yes. Right.

MS. KRAMER: Right.

DR. LO: Yes.

DR. MIIKE: Yes. I caught it. I think I was up at the tail-end of that part.

MS. KRAMER: Right.

DR. LO: (Inaudible.)

DR. EMANUEL: No. The bottom-- Yes. You are right. I didn't update it. Or I may have updated it, but

I now have so many overheads I can't remember.

DR. MURRAY: He changed his mind.

DR. EMANUEL: No, no. I mean, I think the first-- One question is whether these-- We are now comfortable with these boxes, and obviously these two boxes presume something about community consent. We know that, for example, at least at one--(Inaudible.)--to the large commission, Jim Childress raised about whether we use these boxes or not.

But, I mean, we have done some interesting things here. One is we talked about previously collected samples. Sorry.

Another, in this box, in the previously collected samples, was to fuse the clinical and research into one category, not to separate them out. To treat them as the same. To have one set of rules for both.

Then we talked about not how the samples were collected, but how they are going to be used, so that we don't talk about anonymous samples, or anonymizable samples, but samples that are going to be used in an anonymous manner.

I still can't say that.

And then samples that are going to be used in an identifiable manner.

So in this box are samples that are collected with identifiers, but the research is going to be done such that the identifiers are expunged, or encrypted.

So those are, I think--going down--those are the major decisions that, you know, we have talked about. I don't think we have finalized anything, but that is what is here.

And then along this column is these three divisions, which we have had for a while, but have never, you know, sort of had to stand behind.

DR. LO: Zeke, the extreme bottom left box?

DR. EMANUEL: Yes.

DR. LO: You know, what is that supposed to be? I mean, it looks like--

DR. EMANUEL: Oh, I am sorry. This-- I do have-- Too many overheads. Hold on one sec. I have a separate overhead that has it correct. I apologize. Yes. It got shifted over when I made this. It is supposed to be--

DR. MIIKE: Potential harm.

DR. EMANUEL: Just to put this in context, I will move the recommendations off, and just put the empty boxes in while we are talking about the empty boxes-- It is supposed to be community where there are potential

harms. Community--

DR. GREIDER: I recall a discussion about collapsing those two boxes into one.

DR. EMANUEL: Yes. We talked about that about two months ago.

DR. GREIDER: And we are talking about just the outline, and so maybe we could discuss it, in terms of the community things, whether there should be two or one.

DR. EMANUEL: Yes. By going down this way, we may-- I mean, we may begin to feel comfortable that we have made these decisions, which I think in some sense are slightly easier decisions, although one shouldn't minimize it. These are pretty profound changes in the conception of how we are going to deal with things.

And then get to this, which I take it is our intuitions are a little more divided, and we know that there are at least some voices in the whole commission that haven't gone through.

DR. LO: Yes. I missed the last couple of meetings, so I may need to be brought up to speed here.

In terms of collapsing the distinction between samples that were originally collected in the course of clinical care, so the archetypal example would be cancer removed at surgery versus samples that were originally

collected in a research setting, could you review for me the reasoning behind collapsing those two distinctions?

DR. EMANUEL: I think part of the reason, in the previously collected samples, followed the following. In both there wasn't any understanding previously that they would be used, stored and used, for future research where people didn't consent.

And there was a sense, in this case, that the distinction on the rules we might make between these boxes just wasn't significant. There really were substantial differences on the substantive matters.

Now, it may be that we should go through that again to think it through. We have, you know, retained that distinction somewhat here but, again, I think part of, or the main purpose of the meeting is to go through and see whether we still, you know, whether that is really our settled judgement.

DR. LO: Well, just for my clarification, I mean, making things similar can either mean you move this one over to here, or you move this one over to here.

And I guess my concern would be that I have heard arguments that, well, if you consented to have some of your tissue taken for research purposes, it kind of stands to reason that you would like your material to be

used for other research, and so you are probably not going to object if some other researcher comes along with a research project that is really on a very different subject than the topic you originally consented to.

As long as we don't have that presumption that, once you have consented to research we can sort of assume you are going to just consent to any other project, I would feel comfortable collapsing it.

DR. GREIDER: The way that I remember this discussion going, it was more in the other direction in that the kinds of consent forms that might have been used for research and the kind of consent, or lack of consent, that would have occurred in clinical care was so thin that you should consider them all--

DR. LO: To be not consented to.

DR. GREIDER: --as if they really weren't consented for, for future uses.

And that is how I recall the discussion going. I don't know if other people agree with that. And that is why it collapsed more in that direction if there wasn't as much consent going.

DR. LO: I definitely agree with that.

DR. MURRAY: Just to put this in context, very briefly, since I see some new faces--at least among the

faces--I don't recognize among the visitors.

Thanks to the work of some of the people who have helped the commission on this, we know that there are over 200 million identifiable samples out there of human tissue in the United States, of over 100 million different-- Well, 100 million people.

We know that the research--that the tissues--can be used in some very fine kinds of scientific research. We know that people have significant concerns about privacy and confidentiality.

The evidence we have also indicates that most the people, at least who we have spoken, or who have spoken at our mini-hearings, are supportive of scientific research and would like to see research go ahead, thinking that more good will come from it than harm, so long as individuals can be protected against discrimination.

So those are some of the parameters within which we are working right now.

We are talking about stuff that has been collected until now, often, as Carol described, with--you know, this is not to impute the motives of the people who collected it--with a kind of minimal informed consent.

We also know that most people seem to have no recollection--the people we have spoken with--that they

ever consented to the use of their tissue, but in fact you can, in many cases, point to their signatures on the consent forms to indicate that they did indeed consent to those uses.

So these are some of the background conditions under which we are working.

MS. BACKLAR: And I am doing quite a bit of catch-up because I have missed quite a few of these meetings, too.

But, as I was trying to catch-up and read through some of this last night, what I was looking for is what about the issues of people who maybe were decisionally impaired?

And when you are saying that not many of these people could consent, but have we been thinking at all about people who can't consent where their tissue might have been taken? Are we making any allowance for that in these retrospective in collected tissues?

DR. MIIKE: Well, I don't see how we can. You would have to go back to each of these individually, and then I still don't think we get it. So I think we are trying to take a broad hit about what areas where we are not seeking consent--

MS. BACKLAR: Right. I understand. I just

don't want it left out that there is a-- That you are forgetting about a group of people who maybe there was never any consent either, because they--

DR. EMANUEL: Well, someone consented. I mean, generally what happens is someone consented to their surgery, whether they did or a proxy did. And that consent to surgery sometimes contains a sentence and sometimes doesn't that permits people to do it.

So, to the extent that proxy consent for surgery, or whatever else is taken, is acceptable, at least on the clinical side, that is usually--and also on the research side--that usually is--

MS. BACKLAR: How are you going to counter it?

DR. EMANUEL: Well, that is how you encounter it.

MS. BACKLAR: Right.

DR. EMANUEL: I think the general question is, you know, the sort of conceptual framework, and then we can talk about the details of protections.

MS. BACKLAR: All right.

DR. EMANUEL: When we-- Because the framework, I mean, the framework, you know, I think we should be clear. The framework is not value-free. It has got a lot of normative claims in it and, you know, that is

why I think just talking about the outside of the boxes before we even get to the inside is reasonably important.

DR. MURRAY: Yes. We agree on that. Steve?

MR. HOLTZMAN: You know, just to follow on Carol's point, I think--and it touches yours--effectively what we are doing is saying that operationally there was no consent for the extant samples. Just assume that. Against that backdrop, what ought to be done with them?

And effectively the recommendation is to say that, to the extent that research is conducted in an anonymized manner, no consent is necessary, no additional consent is necessary.

DR. MURRAY: I would actually-- I am not quite comfortable--

MR. HOLTZMAN: Putting aside community.

DR. MURRAY: Yes. --with your characterization of it, Steve.

There is research on what informed consent, the process, and what people remember, et cetera. And, you know, sometimes it has been used to claim that informed consent is completely meaningless because people can't recall what was revealed in the consent form often times relatively soon after they signed the form.

I am not sure that is a valid inference from

that, even from that data. To me it may be that someone looks at a question, makes a call, has no objection to it, signs, and that is it. You know, just doesn't feel any need to retain the information.

So I would say perhaps a characterization would be that people, when they were given a choice, had no objection and so signified their consent.

MR. HOLTZMAN: I guess when I said operationally--Tom, I don't disagree with what you just said--but that, insofar as we are not going to require of people, or request of people, an inquiry as to what was the consent, whether there was decisional impairment, whether in fact there was a general consent, whether there was no consent, which is the case with much operationally, we are saying treat them all as if there was none. Now what?

DR. MURRAY: Fine.

DR. GREIDER: I think, again, because we are talking about lumping them all, sort of to reiterate what Steve was saying, if we are going to lump them all, and say any existing samples, then we have to decide what level of protection are we going to have on those, and I think that we are going in the direction of the level of protection that had the least kinds of consent.

DR. MURRAY: Right.

DR. GREIDER: And so, in lumping it, we then go toward the most--

DR. MURRAY: Right.

DR. GREIDER: Sort of the least common denominator in that group that we are lumping together, if we are going to lump them.

DR. MURRAY: Yes.

MR. HOLTZMAN: Or you could go the other way, right?

DR. GREIDER: You could go the other way, but I--

MR. HOLTZMAN: Yes. Well--

DR. GREIDER: --understood all of our discussions in the past going in that direction.

DR. MURRAY: Right.

DR. LO: If I could ask another question about sort of the outline of the grid.

The relationship between the research question and the condition for which the sample is originally connected isn't a parameter in this framework.

And I guess I want to raise the question of might it not be the case that, under these conditions of not having very, you know, sort of thick consent, that it

might make a difference as to whether the research question the researcher proposes to address with these stored samples is pertinent to the condition for which the sample was originally collected.

So, for example, if I come in and have a biopsy done for colon cancer, I think it stands to reason that I would probably be interested in having scientists investigate something that pertains to the diagnosis, pathophysiology or treatment of that condition.

But if someone just said, "Gee, there is this amazing tissue archive and I have a totally different research question that has nothing to do with that condition," are we going to treat those two sort of protocols the same in terms of the level of review?

DR. EMANUEL: I think--

DR. LO: I ask that just because I think the paradigm we have in mind, when we talk about this, I think is the good science, so it is someone saying, "Gee, wouldn't it be interesting if we could find a genetic marker for predisposition of this condition which would lead to early diagnosis of the treatment?"

But I think there also is-- There are a lot of proposals made that I think are either of questionable scientific merit or, frankly, you know, come out of

political or social agendas. And I think, again with genetics, that whole background is-- And I think this isn't just a historical thing.

I reviewed a report Eric Meslin is working on, on the genetic basis of behavior and, you know, there are a lot of studies being done on the genetic basis of antisocial behavior, by which they mean everything from school truancy to arrests for violence.

I could-- One could imagine someone with enough sort of, you know, open-minded scientific agenda pursuing these questions which, you know, are interesting and important questions of ethnic differences and, you know, propensity to antisocial behavior.

And I guess, from the point of view of someone whose samples were originally collected for, you know, the diagnosis or, you know, clinical study of--whatever--heart disease or cancer, it may make a difference as to whether the researcher is proposing to study those questions as opposed to something totally different and, in addition, where the nature of the study of the hypothesis may be objectionable to some people.

DR. EMANUEL: I think we have talked about that and--I will speak for myself--one of the problems is you immediately get into what actually was it collected

for? And this is particularly true on the clinical side where the objectives are--

So here is the example. Here is an example. You went in for a breast biopsy but, like most women, the breast biopsy actually is negative. So was it originally collected for cancer or for breast biopsy? I mean, the category you put it into turns out to be a little vague, or not so much vague as malleable.

Or only in the ones that really were cancer can you test for, you know, cancer. If it turns out to be a benign biopsy, you can't do any cancer research on it? Or, similarly, you know, you go in for, you know-- Is it Tay-Sachs disease, or is it Jewish genetic diseases that you are looking at with those samples?

So the categorization you put it under I think turns out to be something that could be changed or recharacterized and it is, you know, one has to do a little bit of a leap of faith into what was in people's minds supposedly when they consented to whatever the procedure is on the clinical side.

On the research side, we now know, for example, you know-- Again, the examples I like to use are the Physicians Health Study or the Nurses Health Study. They are collected for a very narrow type of research

issue but now a whole slew of questions, that certainly weren't in the minds even of the investigators--you know, genetic test for propensity to thrombosis, et cetera--now become relevant on those samples.

And depending on how you want to characterize what the objective when it was originally collected was, you know, you can either include or exclude those. And I think one of the problems one gets to--

And I confronted this and I reported it to the subcommittee.

When I tried to write a sort of generic informed consent--not for the previously collected samples but for the future collected samples--it becomes very difficult to imagine how you are going to phrase those kinds of-- "I will permit it for this but not for that."

And maybe we have been slightly--I suggested last time--maybe we have been slightly skewed because of the example we have, which I think is a good one, from the National Action Plan on Breast Cancer.

I mean, they start out with a small purview, right? Women who are coming in worrying about breast cancer. So you have got cancer, breast cancer, and then you add onto it genetics or no genetics. But if you are trying to get a generic sample, that anyone who comes in

for clinical care is going to fit into, I think suddenly that paradigm quickly breaks down.

DR. MURRAY: We are going to talk about the future stuff this afternoon so I am just going to--

DR. EMANUEL: I was just using that as an example.

DR. MURRAY: A very good example, and very appropriate.

DR. GREIDER: So, in addition to what Zeke said, sort of how you categorize things, I think that the kinds of concerns that you were raising about the research--that people might have concerns about certain research that is done--that those things I would hope would be addressed at the level of the review of the research or the IRB, or some other panel that is looking at the actual research itself. Rather than attaching it to the tissue samples you attach it to the research.

DR. LO: Yes. I think that is a terrific point.

And so my question then is what mechanism for review of the protocol is there so, for instance, the IRB either gives no or minimal review, or just administrative review. Is that sufficient review of the research protocol?

I mean, if the study is not funded by an agency that has strict peer review, and many of these studies may not be, and if the IRB is only giving administrative or less review, then I think the question is where is that review going to take place?

But I do agree with you that it is not a function of the consent because we are sort of speculating at that point whether people would want it. But it seems to me we would want to have some mechanism for review.

And there I think we are faced with a dilemma of how much are we willing to trade-off for review which may have some delay of research versus no review or minimal review, which may let some things slip by that, in retrospect, after the study is published, people would say, "Well, wait a minute. How come they were permitted to do the study?"

DR. GREIDER: But I think that that is where there are some-- That is why this is structured the way it is. There is, you know-- Are there individual concerns or are there community concerns? And the kinds of things that you are raising I think would fall into the community concerns area.

And so then the question is what do we fill in that box as to what the kind of review is?

DR. LO: Right.

DR. GREIDER: But I guess we are discussing the framework. First, we will go through the framework and then we will go through-- Hopefully we will get to filling in the boxes today.

DR. MURRAY: Steve, then Bette.

MR. HOLTZMAN: You suggested, Tom, we will take up future samples tomorrow; I mean, later today. For those of us who got in at 3:00 a.m.

(Laughter.)

DR. LO: It is tomorrow.

MR. HOLTZMAN: Yes.

But I can't help but wonder, in listening to Bernie's question, if a lot of how we think about the existing samples is not really shaped by how we think about the samples that we will be collected tomorrow.

In other words, if you believe that, with respect to a sample taken tomorrow, there ought to be some consent, that the individual has some say in how it is to be deployed, that, with that background assumption, where your intentionality, your decision-making, all of that can be brought into play, that when we then think about the sample where none of that was in play, you then say, "Well, how can I use it? All of that was absent."

And you start to try to come up with the cases about, "Well, how would I conform with that individual's intents and desires if I had known that?" Which leads you down the kind of path Bernie started down.

So I think it comes from this notion that, with respect to the sample where I did have some control, all right, if you go back counter-factually and say if I had had it, you end up concluding you can't possibly ascertain what the intentions were. And I think that is to Zeke's point.

So you, I think, then have to look at how would we feel-- How do we feel about the samples to be collected tomorrow and how thick is the consent in that instance, which drives you back to questions about what is your relationship to your tissue, and to what extent you should have control over the destiny of it.

Because if you think that that is really, really thick and that there is this ownership relationship, for example, with complete dispositional authority under all cases, you are going to be more troubled about thinner consent in the past.

If, on the other hand, you feel, as reflected in, say, Zeke's example, that we can make distinctions and use mechanisms like opt out, in the case of the clinically

collected sample, you may be less troubled about the thinness or the absence in the consent of the past.

It is just a thought.

DR. MURRAY: Bette?

MS. KRAMER: I think that my concern is that whatever assumptions that we make; that they are very, very clearly stated.

And that if we are going to assume that, in collapsing this in terms of the stored samples, that we are going to assume that any consent that was given in the past was so thin that we would not regard it as adequate going forward but, you know, in an attempt to allow the scientific research to continue to go forward, that we are going to, you know, we are going to make these rules. We are going to go work on that assumption.

But state it very, very clearly up-front and probably include language that calls for a high standard of review of any protocols that will be using this research, fully understanding that a consent--an adequate consent--may not have been given. So just call for a very high standard of review, I believe.

DR. MURRAY: I want to add something to the portrait of the way things were.

I mean, if I were convinced that researchers

in the past knew that they were going to be using tissues regularly for research purposes and that they could get enormous amounts of personal information out of such tissues, then I would probably insist on very rigorous standards, even for consent for past use of tissues, even anonymous use.

I am not convinced that that is the case. And my sense is that most people-- You know, most of the people know most of the tissue was collected for other than research purposes. Overwhelmingly that is true. They were collected in the course of clinical care.

Collections were built up partly out of legal requirements, to keep for quality control, to keep tissue samples for quality control purposes, and the like.

It is relatively recently that--people--the techniques for pulling information out of these tissues, genetic information, have become, that the techniques have sort of reached a kind of initial maturity. They still have a way to go before this is achieved and is an easy thing to do.

And it is relatively recently that the concerns about genetic discrimination and privacy have been raised to new heights. And, you know, we have people around this table who have been a part of the course that

insists on the importance of protections against incursions on privacy and protections against genetic discrimination.

So I think the past is-- I mean, it is not just that research is valuable, but that I think it was not unreasonable for the people gathering the tissue in the past to think that we are not doing anything all that exceptional, or all that of likely personal significance to the individuals whose tissues are being collected.

I just wanted to say that that is an important part of the background for me. But that won't be true. And it is really at the cusp of not being true any longer, and so we will have to have different rules I think for the past and for the future.

Larry?

DR. MIIKE: First, I want to say hello to Dave who is-- David Cox is sitting at the middle table here.

DR. MURRAY: This isn't even a virtual David Cox today.

DR. MIIKE: A couple of things. One is that, on the issue about past informed consent, I mean, another way to look at it is that it is simply stale. I mean, it was given awhile ago and, you know, just the fact that time has passed.

I just want to react to some of the things Bernie is raising. Maybe I am wrong, but what I hear, and the kinds of concerns Bernie is raising, is sort of outside the box that we are looking at. I mean, it is sort of like what kinds of research should fall under the purview of IRB review? What kinds of things should fall under the federal agency type of review?

Because you are raising concerns about shady research, or research outside of these areas. And it seems to me that we really can't address it in what we are dealing with right now. And now we are sort of very, very focused on the consent issue around the whole issue about research on samples.

So am I wrong or, Bernie, are you raising some of the issues that I think are really outside the discussion--the framework of the discussion--that we are trying to have?

DR. LO: Well, I guess what I am saying is that, if we only focus on the consent issue without attention to the larger question of whether the research is appropriate and should proceed, I mean, consent is only one of the mechanisms by which we judge whether or not we think a research protocol is appropriate and needs to proceed. And I think it is hard.

I mean, as some people here were saying, I think that, to the extent that we have questions or reservations or just don't know about the quality of consent, one may want to look at other mechanisms, such as either IRB review or community review, to satisfy us that we feel comfortable that the research ought to proceed and, you know, meets some ethical standards so that--

Although I think, you know, it is important to look at the consent issue, I am not sure we can view it in isolation with the other tools we have to review research.

DR. MIIKE: Well, I agree with that.

But the way that I have been looking at it is that you sort of-- We can't move and look at all those things all together and try to change the IRB--we are going to talk about the community consent issue later on-- but the issue about whether it is a legitimate research or not isn't just applicable to tissue samples; it is across the whole research spectrum obviously.

MR. HOLTZMAN: Unless Bernie is saying something along the following lines; that there is a set of research activities which, if individuals consented to them, they are okay. All right? But in the absence of consent, one would question whether or not they are okay.

So there is research beyond the pale, there is

research which is scientifically wonderful and, in between, there is a sense in which that, in that kind of research, one ought only be part of it if one has specifically consented to it.

DR. MIIKE: Yes. But, Steve, I mean--

MR. HOLTZMAN: But I--

DR. MIIKE: But, Steve, who would say, "I consent to a bad research on my tissue?" I mean, you know--

MR. HOLTZMAN: No, no. It is not-- I don't think it is an issue of bad research. I think it is an issue of, if one--

I am not saying that this is easy to do, or one ought to do this. I am just trying to frame for myself what Bernie is saying.

That there could be a scope of research activity where reasonable people could say, "Well, maybe Zeke would be interested in participating in that, but I am not." Okay? It is not bad; it is not good. Just a difference about whether one wanted to participate in that kind of research.

And if one could say that falls within that--all right?--then that would be the sample, the kind of thing that Bernie would be pointing to. I am not sure it

is doable.

DR. MIIKE: But I don't think that is what he was raising.

MR. HOLTZMAN: Well, I will ask him.

DR. GREIDER: Let us ask Bernie.

(Laughter.)

DR. GREIDER: We need to--

(Simultaneous discussion.)

DR. LO: I mean, I think the harder questions are more in the gray zone as opposed to beyond the pale.

I think that there are some types of research that some individuals may not want to participate in, but since we don't know--we couldn't ask them way back then and we couldn't have anticipated what the questions are--I think we may want to find some way of looking at the question as to whether a significant number of people who were included in this tissue bank might have had objections.

I think another way to look at it is when you consent, particularly in the kinds of, you know-- Even the good consent where you go to a hospital, you trust your surgeon, the surgeon actually does talk to you about, you know, "When I take out the tissue we are going to use some of it for your diagnosis but we would like to use--

The standard routine is to archive part of it for all kinds of research." And then explain to you the kinds of studies that are usually done.

It seems to me part, to the extent the consent had any meaning, you had some idea that good scientists would be doing it, they would be working on important research questions in a rigorous way. And in a sense I think you consent, to the extent that you consented at all, to that quality of the study.

But then the question is, when the protocol comes down the road 10, 15, 50 years later, what mechanism is there in place for assuring that all those criteria are met?

And I just think that, if you look at the current federal regulations, there is a lot of sort of ways you can have research get through with minimal approval that, frankly, I don't think any of us would want any of our staff or people under our supervision to be doing. So I think that is my level of concern.

That if we can't, because of the way the consent was obtained or not obtained in the past, you know, really say the people wanted to do this and they kind of understood what was involved, and there might have been some concerns and objections, but they nevertheless

went ahead, if you can't say that, then I think I want to look even more closely at the other mechanisms we have, as are these, you know, other lines that Zeke had in there with regard to the IRB review or, as we are going to talk about next time, the community consultation.

DR. EMANUEL: I think it is helpful here to stick to the divide between the tissue to be used in an anonymous manner and an identifiable manner.

Let us remember, on the identifiable side, I think our general intuition for everyone in the room has always been that full, informed consent, you know, even if you are using a previously-stored sample, has to be obtained from the people. So this issue of consent doesn't-- Our debate doesn't apply there because we agree you have to get consent for that. So we are really now into the tissue to be used in an anonymous manner.

Now, within those boxes, it is important to think through that traditionally there have been only two types of protections.

One protection is lumped into the IRB. You know, is this a valid study? Are they going to get useful information? Is the question not harmful?

And then there is the second level of protection, even if all of that is true, "I have the right

to consent or not consent to participate in that study."

In the already-collected samples, the problem arises because that second level--the consent level--doesn't exist. And I should remind us--again, jumping ahead to this afternoon because they are not all that separable--even in the samples to be collected in the future, we recognize that you are not going to be able to have detailed informed consent. You are just not.

Full informed consent is not a possibility because today we have samples that are, you know, 75 or 100 years old and, in the future, they are likely, you know, if I get surgery today, you know, the day after our sample that--who knows?--it may be 100 years before someone decides that Ezekiel Emanuel's, you know, pancreas or lungs or heart--or whatever it was--might be useful.

DR. GREIDER: Brain.

DR. EMANUEL: Brain. Yes, right. That they know is not useful. There is not a cell left.

MR. HOLTZMAN: (Inaudible.)

(Laughter.)

DR. MURRAY: I want you to notice it is not even 8:30 in the morning, and they are insulting each other.

DR. EMANUEL: You need a little more caffeine

in that coffee.

(Laughter.)

DR. EMANUEL: So I think we have to operate under the assumption that consent just isn't a good--or isn't sufficient here--protection.

Now, some of that is for practical reasons; some of it may actually turn out to be, you know, more comfortable for philosophical reason, separate from the practical concerns.

And then I think you are right. Then we have to be reflective and look back on the other kinds of protections. The traditional protection of the IRB is one.

And I think what we have been discussing for the last few months has been do we add a level, another level, of protection that doesn't even exist in the common rule now, which is this community? You know, granted it is vague, it is mushy, it falls between the fingers, but we think somehow it is very important.

And I think in part we think it is important because it addresses really, at least to some extent, the concerns you have. If this research really has a potential to be stigmatizing and down-right harmful, then we are not even satisfied with the IRB. You know, they

have-- We want to think about adding another level.

But I think-- I do think, following up on a number of comments here, we really do need to get out of the consent box because we just can't satisfy it here, even if we wanted to. It is just not going to be possible in those tissues where it is to be used in an anonymous manner, without I think really grinding the whole system to a halt and harming things in a way we wouldn't want to.

So I don't think consent is a-- We shouldn't rely on it as a safeguard at all. And I think, in some ways, it may be more an informational process than a real safeguard.

DR. MURRAY: Bette?

MS. KRAMER: I think Zeke has probably already said it--

DR. EMANUEL: Oh, I am sorry.

MS. KRAMER: No. No, no. Not at all. Well done.

DR. LO: Can I raise another question in terms of concerns one might have of doing research in stored samples? I need to defer to the scientists here.

Is there any sense that you may run out of the sample? That if you only have, you know, a couple of tubes and people in 1997 are doing all these studies, by

the time someone has the definitive DNA probe, in 2005, there may not be enough samples?

And how do we factor that into this kind of analysis in terms of appropriateness of research as sort of the big question? So I know Carol would be the best person to ask.

DR. GREIDER: With any given sample, of course, you would worry about running out of the sample. But I think the kinds of things we are talking about here when we have, you know, 100 million samples out there, most studies that are done, you know, you are going to use several thousand to, you know-- You are not even going to get to the 10,000 level. And so I don't think we are concerned about depleting all--

DR. LO: How about a more specialized sample like pedigrees of--

DR. MURRAY: Well, I think Jack has a good example. It may be useful to hear from him.

DR. KILLEN: Yes. Jack Killen. I am from NIH, the Division of AIDS.

I think there is a few that just spring immediately to my mind. I am speaking from the perspective of prospectively assembled collections done for research.

Certainly in the case of HIV, there are millions-- We have millions of samples already stored away in a repository. But about 90 percent of our requests focus on about 1 percent of the samples. And, yes, running out of them is a very big issue.

One of the things that we have started doing is generating immortalized B cell lines as a way of getting a reproducible supply of DNA from the individual into the future.

The process of going through the decision-making about whether or not that was good maybe we can talk about later on in the community consultation part.

Is that, Zeke, what you are referring to?

DR. EMANUEL: Yes. An exact example, which I think is a helpful example. Running out of cells and then the decision to make them immortal so that you can, in the future--

And, I mean, I think it is inevitable that there are going to be some tissue samples, for whatever reason, that turn out to be very, very valuable, either because of the combination of clinical information or because there is something unique about this set of people separate from even doing it in an identifiable pedigree manner; just, you know, you have collected 10,000, and it

happens that all the relevant diseases you are interested in, you know, turn out to fall into a small group.

But fortunately there are techniques at least that may, you know--immortalization--raise certain questions. You know? Does anyone have the consent for that? In what manner might they consent? But it does somewhat obviate the issue of are we running out of tissue permanently?

DR. GREIDER: But that is only for certain kinds of tissues though.

DR. EMANUEL: Right.

DR. GREIDER: We can't immortalize--

DR. EMANUEL: Cell blocks.

DR. GREIDER: Right. Or certain tissue types, too.

DR. EMANUEL: Right.

DR. KILLEN: Or certain research questions.

DR. MURRAY: Well, how are we doing on the overall structure up there? Do we agree? What are the key choice points? Let us see.

Are we agreed that, for existing samples, we are not going to make-- We are not going to claim the distinction is important between those collected for the expressed purpose of a research proposal versus other

purposes, if that were--

This is a very indirect way of saying it--I apologize--but we are going to say we are not going to observe that as a significant distinction? Is that right?

(No response.)

DR. MURRAY: We are going to treat them as effectively the same for our purposes. Is everybody comfortable with that? Do we have a good argument for that? Do you feel we have a good argument for that? Okay.

We are also not going to pay attention to the specific terms of the-- Well, that is-- Let me put that a little differently.

We will pay certain attention to the specific consent that may have been given or withheld if-- I mean, I think we need to state that, right? If someone has said, "I don't want my tissue used for research," in my view that should be a veto. That tissue is not used for research. Do we all agree on that?

(Whereupon, there were several affirmations.)

DR. MURRAY: If someone has said, "My tissue should not be used for research of this kind," do we all agree that that should hold? People should have the right to veto it. If there is a record of any kind of objection

of that sort, that must be observed is my-- I think that is a very clear view I have.

But, in the absence of such opposition to research, we are going to--in the past, again--we are going to assume that, you know, barring evidence of some malicious motive on the part of the gatherer of the samples, that the samples ought to be at least possible to be used for research in an anonymous manner.

Do we also agree that any research that would include identifiers must--even samples collected in the past--must include prospective consent? Are we saying that? You must go back and get the individual's expressed consent to do it if we are going to use their samples in an identified manner.

I can think of one case, one set of cases, where that might be a problem.

DR. GREIDER: We really haven't discussed the identified stuff. I thought we were pretty much in the anonymous box so far.

DR. MURRAY: Yes.

DR. GREIDER: I mean, to back up a level, as Zeke had pointed out, it is somewhat different to say research, how the tissues are to be used as opposed to defining the tissues.

So at the second level up there, to be used in anonymous manner and to be used in an identifiable manner. Right? Maybe we should agree--

DR. MURRAY: On the anonymous.

DR. GREIDER: Maybe we should agree whether those categories--that that framework--is the one that we want to adopt and say it is how the research is done, not the actual tissues themselves.

DR. MURRAY: Oh, we have accepted that. That is-- If I got that wrong, I apologize.

It is how the tissues are to be used because we are going to assume that most of these tissues are-- They exist in some state in an identifiable way. That there are identifiers linked and we are going to have to create a recommended structure of a kind of stewart of the tissues who will then forward the tissues and other information, as appropriate, but stripped of identifiers so that you can't walk back and find out who the tissue came from.

DR. GREIDER: Okay. So you are just assuming that whole discussion from the past?

DR. MURRAY: Well--

DR. GREIDER: I just am trying to go through and-- You know, since we are sitting around the table

here agreeing, do we agree to lump, yes or no? And we just said yes.

DR. MURRAY: Right.

DR. GREIDER: Then the next level is do we agree that this is how we are going to deal with the tissues? And then it is how the research is going to be done.

I personally do agree with that category, but I don't know that we have sat around and had that agreement at the table.

DR. MURRAY: That is a good point. Let us find out if we agree with it.

DR. EMANUEL: I might say that, I think, is a very important reconceptualization to the way the debate has been held.

If we remember back to the arguments between--I hate to be so crude--but Cord and Clayton and, you know, the American Society for, or the College of American Pathologists, the ELSI Working Group, et cetera, they focused on the sample nature, and we are re-doing it to say it is really not the sample we are interested in; it is how the research is going to be conducted. And I think that is an important break.

We have discussed it a number of times, but I

think it is, you know-- Because it is important, we should really be very self-conscience about that change.

DR. GREIDER: And we should highlight the reasons in the report as to why we are considering reconceptualizing that.

DR. MURRAY: Right.

DR. GREIDER: Or why we did reconceptualize it.

DR. MURRAY: Yes. And this is sufficiently important. It is worth making sure that everyone on the commission is fully comfortable that they understand the distinction and believes it is the right one to make.

DR. LO: Let me--

DR. MURRAY: If this is a time when you have any uncertainties, you should speak up please.

Bernie?

DR. LO: I actually don't personally, but I guess since we are saying this is an important reframing of the issues, maybe we should just sort of think back and how would-- What would the objections be to this? How would someone like some of the people in the ELSI Working Group respond to this proposal? So if we can anticipate what some of the rebuttals and objections might be, that might be helpful.

Because I agree. I think this is very important. I actually think it is a very useful step. I mean, maybe we could float this by Clayton, or some of the people in that group.

DR. EMANUEL: I mean, I think part of what is going on here is the idea that we feel somewhat comfortable that you can, even though the tissue itself is labeled, you can--

The researcher will get it in an anonymized manner; that they can't walk backwards to identify the people; that the potential harms that are present therefore are obviated by that kind of protection; that the concerns one might have about identifying a community are taken up in a different way, not by focusing in on whether the sample has got a label or not.

I mean, I think those are some of the rationales. At this hour, I am not sure I can reproduce all of that.

MR. HOLTZMAN: Can I--

DR. MURRAY: Yes. Trish and Steve.

MS. BACKLAR: I just want to say again, as you went through this list of people who would object, consent, and so on and so forth, I still think you have a tricky area in there at the group of people who may not be

able to consent.

And even though Zeke said there would have been a proxy, and so on and so forth, it could still be a little sticky. I think that you have to identify that group as you are going through; people who say no absolutely. You understand that you are not going to do it and--

You made a list of people who would consent or not consent and how you would deal with that. And I just want to make sure you keep the decisionally impaired in there in some way.

DR. MURRAY: Trish, I think I will count on you, when you think that quite a different policy or set of rules ought to be enforced for people who are not decisionally competent at the time that the tissue was taken--which would include all children and would include all adults who are unable to give full informed consent--to signal that; when you think it actually makes a difference in how we ought to treat those.

I haven't heard that yet. I have heard you say be conscious of it. But if you see a point where you think it makes a substantive difference in the rules we ought to propose, please say so.

And have I missed you? Have you indicated

that already?

MS. BACKLAR: I wanted to say that I was concerned that they were left out in your list because it may alter the rules--

DR. GREIDER: What I understood--

MS. BACKLAR: --in some way.

DR. GREIDER: --Tom to say was, if there is something contrary already written down in paper that is collected, we are not going to ignore that.

Is that not what you were saying? That there was already somebody going on the record in paper saying, "I don't want my tissue used for that."

DR. MURRAY: Yes. And that is it. End of story.

DR. GREIDER: And that would include decisionally impaired as well as--

MS. BACKLAR: That you wouldn't use their tissue.

DR. GREIDER: That is right. That is whatever is already written down will be followed. But we are just making the assumption that a lot of things weren't written down, and so you might want to have additional protections.

MS. BACKLAR: Right. And that--

DR. GREIDER: So I didn't hear Tom excluding the decisionally impaired in any way. I heard him say--

MS. BACKLAR: But they might fall into the group where something was not written down.

DR. GREIDER: And so that is the best--

DR. MURRAY: Which is going to be overwhelmingly the case for--

DR. GREIDER: That is the--

DR. MIIKE: Wait--

DR. MURRAY: Larry?

DR. MIIKE: I don't want the exceptions to the rule, our general rule. I think that, for previously collected samples for which there is no indication about not wanting to use the tissue for research, I don't know how we can go back and ask on an individual basis.

On the looking forward side, clearly we are assuming that someone can give informed consent. If there are issues raised about their ability to give that, then that falls within that purview, so when we say that there will be informed consent, it doesn't mean it is an automatic process; it means that they can really give informed consent.

So when we get into the discussion this afternoon, those are the kinds of areas that we will be

looking toward your group to tell us whether the, you know-- I mean, you can sort of overlay your structure on top of ours in terms of the prospective type studies.

DR. MURRAY: So let us-- Trish, keep raising the issue of decisionally impaired persons because we want to ask at each point does it make-- Will we want to sort of make a special provision or special rule or other treatment of such persons?

At this point, as I understand it, we would treat all samples which have been legitimately obtained--and I am being purposefully vague about what it means to be legitimately obtained--in the past, previously collected samples, we are going to treat them all the same way.

We are going to look to see if there is any opposition to research, in which case there will be no research on that sample. We will look to see if there is a specific opposition to specific kinds of research, in which case there will be none of that research on the sample. But otherwise we will treat them pretty much the same, I think.

If you think that is inappropriate, we need to hear that and we need to hear why.

It will be different I suspect as we go to the

samples to be collected hereinafter, where consent will be, you know, we will be able to hopefully have a more informed, more robust kind of consent. Not perfect, but--

DR. MIIKE: Even in the second column, where we determine that previously collected, you know, but still identifiable, then this same issue comes up.

DR. MURRAY: Yes. That is--thank you, Larry--that is absolutely right.

Steve had his hand up, and then Rachel.

MR. HOLTZMAN: I think in moving to the distinction, where we have moved of not the condition of the sample but rather the kind of research, as we are writing that, I think it is worth reflecting on whether, in fact, we have moved very far from where historically the reg was, because one thing that struck me when I read the Clayton paper is I thought they had taken the reg and changed it in their mind, intentionally moved from a standard which had been research conducted anonymously to the sample itself.

So I don't think we need-- We shouldn't immediately assume that we are, in fact, changing the way this has traditionally been thought about, which is one comment.

The second thing is, in focusing on research

conducted in an anonymous manner, we should be clear on what we mean by that.

For example, do we mean that the individual conducting the research can't hook up the research to the individual or that, say, the publication is not one from which one could discern the individual? And I think we should just be clear on what we mean by that.

And I think we mean the former and therefore, by definition, the latter as well.

DR. MURRAY: That is my understanding. Does everybody share that understanding; that, once the tissue and whatever information goes forward with it, that it would be practically impossible to walk back and find out who it came from, so the researcher would not have the information.

MR. HOLTZMAN: So is that practically--

DR. GREIDER: That is my understanding, yes.

MR. HOLTZMAN: Right. Because then that practically raises the sort of thing the theology group talked to us last time about which is that, if the pathologist is to be the researcher, then they need to go get someone else to be the stewart effectively.

DR. MURRAY: Yes.

DR. GREIDER: Yes.

DR. LO: Is it what you intended also, Zeke?

DR. EMANUEL: Yes. I think that is quite good. The researcher has to be blind.

DR. MURRAY: Right. Now Rachel and then Bernie.

DR. LEVINSON: Just very quickly, because we were talking about special groups, I just want to raise the question of the dead when you are talking about retrospective studies, not because those should necessarily be treated differently under the boxes that you are defining, but because they are currently treated I believe under the common rule very differently, and so you would be making a change to that that you should keep in mind as you think about the recommendations.

DR. EMANUEL: I think actually that is important especially when we get to the identifiable because, if they are dead and we are going to use them in an identifiable manner and we require full informed consent, we have a problem.

But that is a very-- I mean, that is an important category especially since probably the vast majority of our current samples actually do come from people who are currently deceased.

DR. GREIDER: Can I just ask how are they

currently treated differently if they are dead or not, under the common rule.

DR. LEVINSON: Exempt.

DR. MURRAY: Exempt from IRB review. Is that right?

DR. LEVINSON: If they are dead?

DR. GREIDER: Yes.

DR. MURRAY: Anonymous or--

DR. LEVINSON: Not specified.

DR. GREIDER: Really?

DR. MURRAY: I think-- Yes. I think in all cases.

DR. LO: If I could just follow on one of the points Steve made. I think that what I understand will emerge from our discussions is a rather sort of high tech foolproof way of making samples anonymous to the researcher. And I think we want to distinguish that between much more informal ways of "unlinking" samples which, in fact, are of varying protection.

I mean, you know, if my close colleague in the office next door is the person who does the coding, I don't think that should count as anonymous for the purposes of research.

And, as some of you were saying before the

break, given that the technology now exists to really make it anonymous to the researcher, we should insist on a sort of fairly rigorous standard for doing that.

DR. MURRAY: I can't help this. It is an irrelevancy, but I am going to take the prerogative here.

When Rachel talked about, you know, working with tissue samples, et cetera, from the dead being exempt from IRB review, it reminded me of a colleague--a friend of mine--who years ago was the editor of the medical section of the Encyclopedia of Texas History.

And he and a group of research assistants went out and interviewed eminent but very aged physicians in the State of Texas. They had a rule though on this encyclopedia. When it went to press, they would only publish biographical essays of people who were dead. So at that point I said, "Ah, perish, then publish."

(Laughter.)

DR. MURRAY: So sorry. Who is next?

DR. MIIKE: What I was curious about was what Rachel had raised. Because clearly there still can be harm to family members, and there is the interest of the family members, so are we just going to assume that informed consent must be obtained and not get into the difficulties?

I mean, you know, I am sure there is some protocol that says who you go to first and et cetera, et cetera. Because if we apply to people who are dead and their tissues are stored some people are going to be asking, "Well, how do we address that?"

But do we want to explicitly address it in the report or we just--

DR. GREIDER: Which box are you talking about?

DR. LEVINSON: Yes. What are you--

DR. MIIKE: Well, I am talking about identifiable dead person with explicit informed consent. And I assume there is a proxy. If we are going to insist on that, the assumption is there is potential harm or interest by family members or relatives.

DR. GREIDER: I think we have to go through all the boxes.

MS. BACKLAR: Right.

DR. GREIDER: I mean, we have to start filling the upper right-- We haven't filled in really any of the boxes. It is hard for me to--

DR. MIIKE: Well, I went under the assumption that--

DR. GREIDER: The bottom right--

DR. MIIKE: Yes. I know, but--

DR. GREIDER: --box without having gone through all the--

DR. MIIKE: I know, but what Zeke proposed was-- I didn't see any objection to that, even in past stored tissue samples. If it is identifiable, we are going to try to get individual informed consent from it. I haven't heard anybody say no to that.

DR. GREIDER: I don't think we have agreed to anything in any of those boxes. I certainly haven't--

DR. MURRAY: We are still--

DR. GREIDER: --agreed to what is actually in the boxes.

MR. HOLTZMAN: But we could take Larry's generic suggestion. If, for any box in which we say an individual's consent is necessary, then, if we are dealing with the sample from a dead person, then that consent should be obtained from whoever is the relevant guardian, et cetera.

DR. MIIKE: My second follow up to that is that you clearly have to make a reasonable attempt for-- If a reasonable-- What is the end product of trying to do a reasonable attempt and you are negative in it? Okay. Then do we have to-- They cannot do identifiable research? Do they have to do it anonymously? Or is it,

you know, is it an absolute?

DR. MURRAY: Right. Those are important questions, and I think we will need to come back to them pretty quickly.

But I still want to get to if we have the-- I want to ascertain whether in fact we have full agreement on the elements of the framework.

And one of the key elements we were just talking about was that we will view-- Whether or not a tissue is anonymous is, in our view, with respect to its use in research, not with respect to what may lie in some tissue bank somewhere, but in terms of what the researcher might see.

And I take it that there is full agreement? It is not just agreement; that we actually have very good reasons which we will state for why this is the appropriate way to think about it.

And I think Zeke is right. This is a change from the way it has typically been conceived, but I think it is actually-- It is the way it ought to be done. I think we have actually made an advance in coming to think of it this way.

Now, there are cautions to be born in mind. There are ways of using fragments of information,

particularly information that can be then sort of linked information, electronic databases, to do a certain amount of walking back, so we need to be very conscious about taking the technical issues seriously.

We are not technical experts and I don't propose that we are going to-- I think it would be unwise for us to recommend a particular encryption scheme, or something, but to signal what we think the right principle is, to remind everyone, you know, that this can be a difficult thing to do properly, and that it ought to be done properly, and then to suggest perhaps some procedural mechanisms for how that might be looked to.

MR. HOLTZMAN: So is this the place where we should flesh out a little more about anonymous such that, for example, we intended that there could be continuing epidemiological information flowing in one direction; that that does not compromise, in the relevant sense, anonymity, and that we left open whether, under any conditions, one ought to be able to go back in order to reveal to the subject results.

DR. EMANUEL: I propose we go down the left side of the column first.

MR. HOLTZMAN: Okay. I didn't know if that is built into the question of what is it to be conducted

anonymously. That is why I am asking that question here.

DR. EMANUEL: I don't think so yet.

MR. HOLTZMAN: Okay.

DR. EMANUEL: Not yet.

DR. MURRAY: Questions we need to address. I agree with Zeke that--

DR. GREIDER: Why isn't that the upper left box? What Steve just raised.

DR. EMANUEL: Wait. You mean this box?

DR. GREIDER: Yes.

DR. EMANUEL: It is this box, but I think--

DR. GREIDER: Oh.

DR. EMANUEL: I suggest if we do these three things--

DR. GREIDER: Yes.

DR. EMANUEL: --first because they actually turn out to be also controversial and a new addition certainly to the common rule. And I think if we have all the outside, while it won't be easy to go through the inside, at least we will be very focused. That would be my only suggestion.

And, in part, because we already have had controversy from the full commission, at least on their additional gut reaction without, you know, our explaining

the framework in any detail, or the rationale, to a three-level divide as opposed to just a two-level divide.

DR. LO: Do you want to turn to whether we want the three levels; three rows rather than two? Okay.

MR. HOLTZMAN: Let me just get clear why I asked that question there again. Do we mean by conducted anonymously; something can be conducted anonymously even if there is additional information about the sample over time flowing through?

DR. GREIDER: Yes.

MR. HOLTZMAN: We agree with that. So that does not compromise the concept we are trying to articulate here.

DR. LO: We talked about this last night.

DR. EMANUEL: I think this is the question.

MR. HOLTZMAN: I am trying to stay in the outside boxes.

DR. EMANUEL: Right, right. I understand. But I think the question is, again, one shouldn't-- We shouldn't focus in on somewhere does that information exist with an identifiable label.

The question is, when it gets to the researcher and the researcher is doing it, is it in an anonymous manner such that it can't be walked backwards?

If you can guarantee that, despite a constant flow of updated clinical information--the researcher doesn't know who it is, can't walk backwards except maybe with some safeguards which we can talk about, and the research is going to be done in an anonymous manner--that is what qualifies it as being done in an anonymous manner, not how the sample is, where the clinical record is, et cetera.

MS. KRAMER: But at some point we are going to discuss the criteria that we want included for this encryption, without describing the exact method, right? We are going to address the question?

DR. EMANUEL: I think inevitably, you know, and as I have heard it--and this is just my synthesis of our conversation--we are a divided subcommittee on it. We haven't really debated whether, you know, if you find some, serendipitously find some important information that is relevant to the health of the people, you should be able somehow to break that code.

MS. KRAMER: Well, I don't know so much that we are divided as I think we haven't fully discussed it yet.

DR. EMANUEL: Right.

MS. KRAMER: Right.

DR. EMANUEL: But I think I hear people's intuitions being on different sides. That is all I mean by divided. I agree. We just haven't had a thorough thrashing of that issue which would tell you whether that is going to be, you know, potentially permeable in the other direction or not.

DR. LO: Well, I guess one procedural question is do we want to enter into that discussion now, or go back to the framework and try to see if the grid for the framework is-- Because I think it is something we are going to have to address.

MS. KRAMER: Right.

DR. LO: It is really do we do it now or later?

DR. GREIDER: Well, I mean, it is coming up now. We are going to have to do it today, right?

DR. LO: Do you want to do it now?

DR. EMANUEL: I prefer to do it later.

DR. GREIDER: You prefer to do it now?

DR. EMANUEL: Later.

DR. LO: Later.

DR. EMANUEL: I think we need agreement either to collapse or to retain the three levels of--

DR. LO: Procedurally, how many people want to

defer this until later and move on to the sort of grid as it stands?

DR. GREIDER: Yes.

DR. LO: Yes.

DR. GREIDER: Move on.

DR. LO: Move on. Okay. So we will come back to this later today. Steve, we will count on you to raise it because I think it is a terribly important question.

With regard to this grid, I think the question that we need to look at is are we happy with the three rows, or do we want to collapse the bottom two into one?

Zeke, do you want to--

DR. EMANUEL: Well, I think the other thing we need to be very, very careful about is that, in the current standard, the bottom two rows just don't exist.

DR. GREIDER: Don't exist at all.

DR. EMANUEL: So the first-level question is are we all comfortable with raising, or adding, or elaborating a row that recognizes community harms, potential community harms, or potential community implication?

And then, if we recognize that there is potential community implication, and we are not just dealing with isolated individuals here but connected

somehow with relevant characteristics, do we then feel that this divide, where some of the research even though it identifies a community, may not have any potential harm that we can think of or that it has a harm?

DR. LEVINSON: How can ever say that there are no potential harms?

DR. EMANUEL: Well, I mean, we have tried to think of some examples, and I will just give you the examples I have heard from the research community.

You know, the ear lobe. That is yours, right? Carol's ear lobe example. You know, you are interested in ear lobe design, or structure, or eye color, or things that-- Or baldness. Things that might not have real harms.

DR. LEVINSON: How do you know that the gene coding for the ear lobe is not going to be found later on to have some behavioral implications?

DR. EMANUEL: But you wouldn't know that now.

DR. LEVINSON: But that is--

DR. EMANUEL: And so, therefore--

DR. LEVINSON: But that is not a-- But it is still--

DR. EMANUEL: No. But then, even if you got community consent, you couldn't even talk about it to

them. I mean, it wouldn't effect you if-- I mean, of course, down the line, some information, but that is not going to effect-- You know, do you go ahead with the research now? Because no one knows about that kind of information. I mean, that wouldn't--

That wouldn't be relevant to the consent, right, Rachel?

DR. LEVINSON: No. Only to the extent that the anonymity might be effected. You know, whether someone would be concerned about what the implications of that study could be later on.

DR. EMANUEL: But this--

DR. GREIDER: But this is anonymous. It can be anonymous. You can have anonymous research.

DR. EMANUEL: Let us say you are interested in ear lobe design in Ashkenazi Jewish women. Okay? It is hard to imagine-- Forget future attachments. So you go to the community and say we are interested in ear lobe, the genetic of ear lobe attachment. Okay? And we are going to divide your community up and look for a gene that goes. All right? It is hard to think what the harm of that could possibly be. Okay.

DR. LEVINSON: But--

DR. EMANUEL: Now wait a second. Five years.

You have done the study. You have shown that it tracks with some gene. Five years later you find out that that gene is related to, you know, the high risk of heart disease, or something like that, or cancer, head and neck cancer, or something.

When you went to the community, I mean, do you feel more comfortable because you got their formal sign-off, as opposed to whatever else we are going to require? I just don't see how it would make a difference.

I mean, of course, all sorts of genes that we think are innocuous now might be related to something important, or potentially harmful. I mean, I think--

Remember why we are distinguishing--first of all, why we brought the community in--why we are trying to distinguish these two. We are trying to recognize that there is some category of research which might not, which might have implications for a community, qua community not individually seriatim, and we want to recognize that, especially with genetic research, that therefore the community should have some input as to how the research is done and whether it even goes forward or not.

MS. BACKLAR: Wait a minute. Have we decided that?

DR. EMANUEL: Well-- Okay. But we want some

input, period. All right? And then we will leave it to the extent of the input. But I think the question here is, is it reasonable to imagine that, even if it implicates a community, there are some things which aren't going to--

I mean, what are the harms we are worried about? We are worried about some stigmatization and some discrimination. I mean, suspect categories. Everything is a suspect category.

MS. BACKLAR: I think that Rachel has a very important point. Why are you distinguishing between no potential harm and potential? Why do you have to distinguish? Because, in fact, you don't know what it might be. It simply might be that you are identifying a certain group with a certain shape of their ear and ultimately people say, "Well, that; I don't like that group and it is because of their ear." I mean, their ear shape, or whatever.

DR. GREIDER: But you can't provide for things in the future that you don't know anything about. Right? You can only--

MS. BACKLAR: But my question to--

DR. GREIDER: You can only protect against what we know about.

MS. BACKLAR: But my question to you is why must you distinguish between potential harm and no potential harm?

DR. LEVINSON: It is too nebulous. It is too subjective.

DR. GREIDER: Well, you are going to have to distinguish. The IRB will have to distinguish it at some point, right?

DR. MIIKE: Yes. But, you know, you folks are making-- If you are going to argue that there is no distinction, and I would go along with that, my question would be, would come down on the opposite of where you are, where you would want to have rigorous protections.

And I would argue, if you are going to combine the groups, then my problem is with dealing with communities. What the hell are we talking about when we are saying what is a community?

I mean, you can talk about the Ashkenazi Jewish women as one good example, but if they don't agree in Boston but agree in New York, or in San Francisco, then what is the utility at? But if you are talking about a very localized group of Alaskan natives in a little village, to me that is a community definition that you would want to be very careful about protecting.

So I would prefer to go with the separate of harm/no harm, and I assume that there has to be some group like an IRB looking at it to say whether there is a harm or not, rather than combining both, because if you combine both then I am going to go the opposite way of where you are going to go.

MS. BACKLAR: And also my understanding that you are thinking of this community as different from the Canadian collectivities, which could be families, or can these communities be families?

DR. MIIKE: Well, we--

DR. GREIDER: We haven't said that.

DR. MIIKE: --haven't really said that.

MS. BACKLAR: But that is why I am asking.

DR. MIIKE: Well, no. I think if you are talking about blood relatives, families, no. No. That is more on the individual side to me.

DR. EMANUEL: But wait a second. If you are getting down to families, you are probably getting down to pedigrees which means you are going to be on the identifiable side.

MS. BACKLAR: Right.

DR. EMANUEL: Let us try to keep the boxes clear. I mean, when you get to a small unit such as a

family, and you are going to be doing research on the relationship of the family, I mean this may not be completely--

I see that Steve is puzzled.

But I think that you are probably going to end up on the identifiable side.

I think, again, it is important for us to try to keep some paradigm cases intact. Now, you may be right that the intuition is no matter what it is, if it implicates a group, any group, it is automatically a suspect category.

I personally don't like that idea. I think that is a very bad standard to take. I mean, we do have some suspect, some groupings which, you know, where-- And harms that we are seriously worried about. Harms that could lead to, you know, some form of discrimination or, usually for historical reasons and reasons of social marginalization, stigmatization.

But that doesn't include, you know, every group. And I would remind you that one of the papers I handed out last time, or two times ago--I can't remember any more--was about a study they did out of the Physician's Health Study that identified African-Americans and whites where it turned out that the whites were in a

much higher risk category.

And I had suggested that that ought to fall into community, no potential harms, because that-- You know, you don't usually harm all of such a big group, I mean, of the dominant group. That is just not the way it is usually thought about.

Discriminating against all whites is a very difficult thing to do.

DR. LO: But the other way, if the study had come up the other way, one could argue that, from the African-American perspective, and they said, well, the prospect of discriminating against the whole class is real--

DR. EMANUEL: Yes.

DR. LO: --had the results gone the other way.

So you are going to have to take it when the research was planned, not when the results come out.

DR. EMANUEL: Right.

DR. LO: So, I mean, like any ethnic division is possibly suspect because it could show increased susceptibility among the class, which is already disadvantaged socially and, therefore, adding to whatever burdens and discriminations you have, so at this state it may be a suspect category on the face of it.

MS. KRAMER: The problem I am having, in trying to deal with the decision you are asking us to make now, is that I have great uncertainty as to how we ought to deal with community altogether, and I know that is on the agenda for this afternoon, but I personally am going to have trouble making this decision until we have talked about that.

DR. MURRAY: I am going to ask my fellow commissioners for an act of faith here, which is difficult I know. But it is my faith in Bernie Lo actually, which I don't confuse with any deity, although I think--

(Laughter.)

DR. MURRAY: That Bernie is going to offer us some constructive ideas about how it is that, at least in certain circumstances, one can think about community and get community input into decisions about the appropriateness, design, et cetera, of research.

So let us just-- And if I am wrong, I will tell you. I will be honest with you.

DR. LO: You are wrong.

DR. MURRAY: I am wrong? Okay. Am I wrong, Bernie? I am?

DR. EMANUEL: But I think we--

DR. MURRAY: Seriously, do you think community

consultation is--

DR. LO: I think-- I think-- Well, I think these are very, very tough issues. And I think you are starting to raise some of the complexities. I think what we can do is sort of help begin to sort out. I think, out of whatever discussion we are going to have after the break, we are not going to reach conclusions, but I think we are going to be able to be more aware of what some of the dimensions are, both the possibilities and the pitfalls.

DR. GREIDER: Well, why don't we have that discussion before we decide whether there is one category or two? It seems like we can't make that decision until we have discussed the whole community.

MS. KRAMER: That is what I am suggesting.

DR. MURRAY: I suspect that is--

DR. MIIKE: What I was going to say was that my problem is not with that three-line group with community harm/no harm. My problem is with getting informed consent from communities.

And I think that what we have been seeing--and I think the kinds of things that Bernie has raised--is consultation with communities, wherever you define, is good because it helps to sharpen the focus and make the

research project better.

I have no problems with consultation. I have problems with getting an informed consent out of a group. That is my problem.

DR. EMANUEL: Can I-- I want to raise two points. One is there are huge problems with community, but I want to raise these two points.

One, we are not the first to tread into that pond. Okay? The FDA is already plopped a big stone into that pond and I think, as we have recognized over time, you know, it is an area which we have ignored for 15 or 20 years. That doesn't mean we should continue to ignore it just because it is hard.

Second, I want to-- I think we need to be very clear about distinguishing two things here. One is whether we think that categorization is accurate, and the second level is what kind of protections that entitles you to.

And I don't view-- I mean, we may want to end up saying, you know, we want to recognize this category. We are not sure of the kind of protections, or here are the kind of protections for well-defined communities. This is a concept which is undergoing debate and interpretation now. And our notions of what the correct

protections may be may need to change over time, as the debate gets clearer.

We are going to get a lot more experience from the FDA rule. We are going to get a lot more experience in other areas. And so I think, you know, we need to make this a two-step process.

One is does that divide match with some ethical intuitions, and the second question is what are the regulations that go with each of those boxes? Those are two separate questions in my opinion.

DR. GREIDER: Can you remind me what the FDA stone is?

DR. EMANUEL: Oh. In the emergency exception to informed consent. So you can do a study without the informed consent of the person participating in the study in the emergency room context, if you can't get informed consent because it would delay or harm them; you don't know who to get it from, et cetera, et cetera.

Before you can go ahead with that protocol, you need to get what they call community consent. And they are very vague on what that actually is, what would quality. And it is a thing which, to some extent, they have punted to the local IRBs.

But they recognize that if you are going to be

treating people and you can't get their informed consent, you want another level of protection. I think, in some sense, though not articulated exactly as we have, they are coming to the same kind of conclusion from a different way than we are.

MS. KRAMER: See, given that--

DR. EMANUEL: There are lots of places that are doing it now, but I will tell you what I think is going on in, you know, Boston.

All of the emergency vehicles from one area coming from Brookline go to the Beth Israel Hospital, so if you are going to do a protocol in the Beth Israel Hospital, you go to the Brookline community.

You tell them the kind of protocol you are going to do; that you are going to do it on everyone in the following circumstance. That is a method that you might approach. I mean--

MS. KRAMER: But that is a perfect example. How does one go to the Brookline community?

DR. EMANUEL: Well, I mean, you have got mailings to all the people in the, you know, geography. Right? You might have public forums.

MS. BACKLAR: Advertisements. OHSU is advertising everywhere about this. Little boxes in the

newspaper describing what is going on.

DR. MURRAY: We should just state OHSU--

MS. BACKLAR: Oregon Health Sciences University.

DR. MURRAY: Yes.

MS. BACKLAR: Sorry.

MR. HOLTZMAN: So you are not seeking the consent of the community; you are rather letting them know that a certain practice will be taking place and they should be aware of it?

MS. KRAMER: So it is informational?

DR. EMANUEL: Right. But, I mean--

MR. HOLTZMAN: But they have the opportunity to object.

DR. EMANUEL: Yes. I don't know, you know, I think this is so new people aren't quite sure what happens if the community gets up in arms. "We don't want you doing that with, you know, our people who are coming."

I mean, these tend to be dynamic processes. They don't tend to be, you know, all we are doing is shoving it out there.

MR. HOLTZMAN: So, if I could come back to what we mean by community without getting philosophical, just what we meant here, and explain my puzzlement.

Under the current rule anonymous, or anonymized, or whatever, refers explicitly and only to the individual, so before we even get into lines 2 and 3, there is the question are we going to introduce another line or lines?

And that is that we believe it is a relevant consideration to ask, with respect to a piece of research which is conducted in an anonymized manner with respect to the individual, of whether that research is nevertheless identifiable with respect to a community, and that we think that that is a relevant question that needs to be asked and answered.

I think that is the fundamental first thing we are saying, which really does raise the question immediately did you mean a community as constituted by some social definition or did you mean it is a community in the sense that it is research which is not identifiable with respect to an individual but it is identifiable with respect to any others, in which case you would then get into collectivities, families, et cetera.

I must admit I always thought that the primary divide we were making was along the latter lines; that is, that while not individually identifiable, nevertheless it is identifiable with respect to others or additional

people, as opposed to definition of community.

DR. MIIKE: Yes. But I always got the notion that, okay, if we are doing studies such as this and it--

Well, let us take the case of breast cancer. Obviously it would not apply to the male members. Right? I mean, the issue was the women altogether in that ethnic grouping. So it didn't seem to me that we were talking about--

I guess what we are talking about is that you have individual research in an anonymous manner where the individual is not identifiable, but the research is conducted such that it consciously looks at a particular grouping.

DR. EMANUEL: But-

DR. MIIKE: It may not be a particular family.

DR. EMANUEL: But, I mean, I think it is important to-- You know, one is you could have a sort of historical traditional grouping like the Native Americans. You might have a geography, you know, the Mayo Clinic area, Olmstead County. You might have ethnic groupings. You might have racial groupings. You might have disease groupings; the AIDS community we sometimes talk about. And then you might have families.

I mean, there are sort of six kinds, and this

is just off the top of my head. I haven't thought it through completely.

Now, I think the issue is, you know, not you do research and it shows up because you have these sociodemographics that tracks with, say, Jews, or it tracks with some racial grouping.

The issue is you are going to that, to a particular grouping for a purpose. I mean, your intention is to identify it within this grouping, either ethnic, racial--it might be geography--for all sorts of reasons. You know, you are trying to highlight environmental issues possibly there. It may be a convenience sample that might have geographic implications, you know, implications for people living in that community.

So I think we need to be open. I mean that is why, again, in the sample where I handed out the papers, the question of, you know, whether doing the study about breast implants in Olmstead County might not qualify here as the community. While they, you know, may not have any geographic or racial, you know, you might find out something about Olmstead County residents. They have breast implants at a much higher rate than anyone else, or a lower rate, or something.

DR. MURRAY: It might be-- I am tempted to do

two different things, and I guess I will do them both quickly.

It might be worth asking what problem our sort of concern with community consultation was meant to address. And I will just state how I see it.

Namely, that there are certain circumstances under which one can imagine that, even if my sample had been rendered anonymous for the purpose of research so no one would know it was me, but nonetheless there might be information about some group or groups to which I see myself belonging to, and which others perceive me as belonging to, that I might find either potentially harmful to that group or, in some way, offensive to that group, even if it didn't result in harm.

We would just object to it. We might object to it for religious reasons or other kinds of reasons about our views about tissue, or we might object to it just because we think those are the wrong kinds of questions for scientists to ask and, in fact, most of the people that are in the group I belong to seem to feel the same way.

That is the problem I took it we are solving. Do we agree at least that is the problem we thought this was addressing?

DR. EMANUEL: Yes.

DR. MURRAY: Okay. Now one answer I guess is to say, well, there is no good way to solve the problem so we will just shove it aside. That is one solution. That is not one that I am prepared at this point to embrace.

I would rather see if there is a way where we can do honor to these concerns about offense and about harm. And that is what the community consultation idea is an effort to address.

That is the one thing I want to do. And we have a whole section of the program devoted to that.

Bernie?

DR. LO: Go ahead.

DR. MURRAY: The other thing is just I want to know if we have sort of reached the point where we have at least agreed on the structure--the framework as he calls it--where we can move on.

Maybe what we should do, if we have reached sufficient agreement on that, we can move on to the question of community consent a little ahead of the schedule, and then come back to the structure and see whether or not we want to have this distinction between harm and no harm.

DR. GREIDER: So agree on the structure, but

don't agree on whether there is four boxes there or six basically?

DR. MURRAY: Yes.

DR. GREIDER: There will either be four or six.

DR. MURRAY: Yes.

DR. GREIDER: So we have agreed on the top part of the structure.

DR. MURRAY: Yes.

DR. GREIDER: But not the--

DR. MURRAY: There is one distinction there that we haven't-- We haven't-- We haven't decided whether we are ready to embrace.

DR. GREIDER: Exactly.

DR. MURRAY: Is that an adequate perception of where we are? Okay.

Let us-- We have a break scheduled in 20 minutes. Are you-- Do people feel the need for a quick break now, and we can pick up community-- I see yeses. All right. Let us take a really-- We are going to have Carol's comment and then we are going to take a really brief break and then come back.

Carol?

DR. GREIDER: Can I just make a plea because

we are going to be discussing this again. Can we number those boxes--can we go one, two, three, four, five, six--with my pen so that we can discuss the boxes.

DR. MURRAY: Only if we do it randomly.

DR. GREIDER: No. I want to--

DR. LO: Do it one, two--

DR. MURRAY: No. I am going to make a suggestion as to how to do that.

Okay. We are going to take a brief break. Five minutes. See you back here. Carol?

(Whereupon, at 9:21 a.m., there was a brief recess.)

DR. MURRAY: Elisa Eisman(?) was good enough to distribute a reprint of an article about stored Guthrie cards, DNA banks, for the commissioners. Thank you, Elisa.

We are going to talk about the idea of community consultation/consent right now. And in less than a minute I am going to turn it over to Bernie Lo who will chair this part of our meeting today.

I want to mention that the issue of community consultation and consent is-- Not only is it not unique to the subcommittee and the FDA, it is not unique to the subcommittee and the commission.

I mean, there is a paper on community involvement in research that--that is in draft now, I gather--that the human subjects research half of the commission is working with, and I have been assured that we can have at least a draft of that paper in advance of our next meeting in January.

So it is important here to let the-- I don't want to characterize one of us as the right hand and one of us as the left hand, but let the other hand know, each hand know what the other hand is doing on the commission.

So it is, as Zeke pointed out, it is not unique to our problem; the concern about community involvement in research. Thank you very much.

Bernie?

DISCUSSION OF COMMUNITY CONSULTATION

BERNARD LO, M.D.

DR. LO: Okay. Thanks, Tom.

The next section is going to try and deal with these difficult controversial issues of community that we were starting to touch on before the break.

And I just want to start by saying that this is an issue that comes up in a lot of research, but it seems to me has particular importance for genetic research because learning genetic information on an individual also

gives you some information about larger groups like relatives and families.

There is actually an interesting sort of example of concerns about the impact of research on the community, even when individuals might not be identifiable, and that is clinical research on HIV and AIDS, where very early on in the AIDS epidemic it was clear that this was an epidemic that disproportionately affected communities, in some sort of loose sense of the term, first predominantly gay men, homosexual men, and then, later in the epidemic, both geographical and ethnically targeted communities in the inner city.

The risks were clear. Early on, there were risks of both stigma and very real discrimination in terms of loss of jobs, housing, education, and the like. And very large concerns that individuals who were identified as being members of that group might have other characteristics ascribed to them; the thought that they might be infectious, contagious, or whatever.

We touched on a number of issues before the break:

Who is the community;

What do you do if the community in New York disagrees with the community in San Francisco;

What do you do within San Francisco when this part of the city disagrees with that part of the city;

Who are the leaders; and,

If you wanted to talk to community members, how do you actually do it?

One thing that I think is important to keep in mind is that the kinds of studies that we are talking about in HIV tend to be prospective clinical trials, where you are testing a new drug or combination of drugs. And I think what has happened is that the real power of the community is in talking about the design of the trial sort of before it is initiated. And kind of the power is not whether they give formal approval to the protocol or not, but it is their ability to sway public opinion.

So if respected voices in the community say that they have serious reservations of a trial, that will really cut down on the willingness of individuals to enroll in the trial so, even though they may not formally sign-off or consent--I guess in Larry's terms--they actually have a sort of I wouldn't say *de facto* veto but something getting close to that.

Over the last decade there has been a lot of energy put into community consultation collaboration with representatives of the community in the actual planning

and design of clinical trials in AIDS. It has not been an easy process. Early on, I think it was extremely time consuming and emotionally grueling. Lots of name-calling, shouting, vegetables thrown at people at meetings, and the like.

But I think in that-- And no one could have predicted at the onset how you would design it. I think it was something that evolved over time as people tried to deal with one study and then another study and began to get a feel for who the other players were. And, I must say, I think a lot of the AIDS activists got very well informed on some of the technical details of the science.

We are very fortunate today to have Jack Killen, who is the Director of the Division of AIDS at the NIAID.

His group has oversight over the AIDS Clinical Trials Group and the community consortium that do carry out the large publicly funded cooperative collaborative AIDS trials. And their group has had a lot of experience with community consultation and trying to both understand community's concerns and address them in the design of the study.

So I asked Jack, and he was gracious enough to come to share his experience in terms of how this is done,

what works, what doesn't, what some of the pitfalls are, what some of the benefits are, and then I think we should have a pretty interesting discussion afterwards.

Jack, we are delighted that you could come.

JOHN Y. KILLEN, M.D.

DIRECTOR, DIVISION OF AIDS

NIAID

DR. KILLEN: Thanks very much, Bernie, and the other commissioners. It is a real pleasure for me to be here. I really jumped at the chance to do this--there is no graciousness about it--for sort of two reasons.

One is because I think we have actually a pretty remarkable experience now of the last decade, which I firmly believe is exportable, and the other reason that I am interested is because we have a huge investment in prospectively collected specimen banks, so there is really two reasons for my wanting to be here.

And then, having sat through this discussion this morning, I must say I envy you all in some ways because I can't imagine that anybody plopping into my day would find it anywhere near as interesting as I found this morning's discussion already.

I am a little off my turf on this and so I am feeling a little disconnected from the discussion that you

have had, but what I do have I think are some thoughts about a model that has operated in HIV research.

I can't pretend that everybody would agree with the model as I am going to present it, which is one of the features I think of this beast, but I think it is pretty close.

Bernie asked me a few questions, which I actually found is a useful framework for sort of structuring some comments. He specifically asked me:

Is it helpful from a scientific point of view;

Is it feasible;

Does it allay public concerns;

What are the pitfalls; and,

What are some of the lessons that could be learned?

I would like to go through those quickly and just make a few comments about each one. But first maybe spend just a couple of minutes talking about what it is that I am talking about.

The-- It is really actually-- I came here. I walked here through the tunnel from the other Marriott across the street where right now today the AIDS Clinical Trials Group meeting is going on.

It might have been a really interesting thing

to do for you all to have a field trip this morning to go see the ACTG meeting in progress because what you would see is probably about 15 percent or 20 percent of the people at the meeting being of community origin, participating fully in the process of this research meeting, which I think is one of my sort of global points about all of this.

And that is that I think at the end of this, when the stories are written, what will have come out of our experience in HIV disease is a somewhat different paradigm of doing research where, rather than the notion of researcher and subject and somebody needing to protect, we have taken probably a first and very crude step toward creating a partnership.

I think it has not, by any stretch of the imagination, been a perfect partnership. It has been really rough. It has been very personal. It has been very messy and so forth. But I think at the end of the day that may be-- I would be-- I will be wonderful if that is where it leads.

The second thing is that I think involvement of community--the second bottom-line point--is that involvement of community is essential. The net benefit has far exceeded the costs. And I can't imagine now, from

where I sit, doing clinical research any other way than involving the community.

So the model that we have basically is-- I will just use the AIDS Clinical Trials Group as a prototype.

The fact that we have community involvement grew out in the mid- to late-'80s when there was a lot of animosity, dissension, distrust of the government apparatus, frustration at the slow progress that was seen to be being made, a kind of an in-your-face attitude on the part of many, the activist community, that, you know, "You guys can't do this research, so we will show you how to do it."

There was confrontation. And basically what they were demanding was a seat at the table; to participate in the research planning and execution process. There was a lot of resistance on the part of a lot of people, but a few folks with some vision said, "What is the big deal? Why not allow them in to the process?"

And what was created, without going into any of the detail of it, is a system where, as I alluded to just a couple of minutes ago, representatives of the community of participants in the research studies are a

part of all of the process, from conceptualization of ideas through the design of the studies, their execution, recruitment at a community level, analysis, and everything in between.

A lot of what we do is multicenter trials. The individual research sites each have what they call a community advisory board, which consists of individuals drawn from their local community--whatever that is--and those community advisory boards theoretically are supposed to meet on a very regular basis.

And I will talk about what they do in just a moment, and answer any one of Bernie's questions.

There is also, above that, if you will, or aside from that, what we call a community constituency group which is, at least in part, drawn from the membership of those local community advisory boards and sort of serves in the capacity of working with the bigger multicenter cooperative group.

The community people are fully vetted members of all of the committees of the cooperative group. The executive committee has two community people sitting on it right at the table. And all of the other research committees and execution committees have community representatives.

I probably don't need to go into any more of the detail. If you have questions about it-- It might be more useful to talk a little bit about what they do.

I think then, to move on to the questions that Bernie proposed to me:

Is it helpful from a scientific view? Yes. Unequivocally in a lot of ways.

There is a "but" that I will come to in a minute.

There is a lot of different kinds of ways that we see that this has been helpful. On occasion ideas of science, ideas of studies that need to be done emanate from the community that don't emanate from the scientists. But there is a lot of other areas where the community participation has enriched the science.

Asking us why we are not collaborating with this other group of people doing behavioral research, and forcing that collaboration, if you will, when it wouldn't be a natural act. Providing--

Particularly important--Bernie alluded to just a minute ago, which is kind of alluding--is providing input on studies and helping in the study design up-front, but also forcing the question of why are inclusion criteria so narrow, listening to the community's needs and

desires. Helping sell studies in the community is a very important thing for outreach, to help accrual retention, if the community understands it.

I think the key in this--maybe the biggest thing that sort of goes out of the particulars of HIV research--is the transparency that we have tried to create, which I think is a really key word.

The openness, the trying to deal with the questions of mistrust by opening the process and saying, "Here it is. There really aren't any secrets. Sit down and look and be a player with us in this." That kind of transparency of the process is very helpful in getting the science done.

There has been a lot of other sorts of things that have spun out of it--changing policy. Inclusion of women of childbearing age in antiretroviral studies is sort of one example. Challenging us all the time on why are you doing things that way. Challenging the status quo.

It is incredibly valuable to have people who are not in some way--and I don't mean this in a negative way, as it might sound, it is just a statement of fact--it is incredibly valuable to have people who don't have a stake in the research other than the knowledge asking

questions about why things are being done the way they are being done. And I think that gets back, in large measure, to the transparency of the process and the building of trust.

And then the other thing that has happened is that people know each other. At least in our environment, that sort of grew out of an adversarial relationship--very much adversarial--it becomes very difficult to demonize people when you get to know them as people. And that works both ways; the researchers and the activists. When you begin to know human beings, it is much harder to read nefarious intent.

I think there is a "but" in this that is important to put on the table. In our experience, I think community perspective can be somewhat short-sighted, or short-sighted from a scientific perspective.

Early on the drive, early on in our thing and in all of this--the activists--the push was how many patients do you have on trials? In other words, how many people do you have getting drug, rather than what are the studies that you are doing?

So the goal kind of became, you know, get a lot of people in study instead of do the best possible science that there is to do. That is not a problem at

this point. That was a transient thing.

I think there has been a lot of really remarkable stuff happen in terms of accelerated approval of drugs. That has come with some cost of knowledge and information about long-term follow up, and we are finding ourselves in a quandary today about long-term follow up of some of the regimens that we are using for therapeutics for treatment. Not that that is bad. Not that it was wrong. But it is just a statement of fact.

And then, finally, I think the community does not have all the answers. The community does not have all the wisdom that needs to be applied. They have a perspective which is part of a multidisciplinary effort.

I think it is practical, very definitely. As I said, I can't imagine-- And I think you have to be imaginative about how you conceive of it, but it is very definitely-- Practical could be done in other circumstances.

There can be difficult transitions. It is costly in time and money, particularly time I think. You have to invest more time in education and you have got to watch your language. You have got to, you know-- Not so much watch your language as watch your jargon and pay attention to it and translate into English, or educate

people about the words that you are using.

And that works both ways also. That works both ways. All this works both ways. I don't mean to sound condescending. I hope I don't.

There have been some really fascinating examples about ethical questions that have come up, and if you are curious about them we can go into them. The ACTG 076 Trial was a perinatal transmission study, placebo controlled, that gave AZT to mothers and pregnant women and proved disruption of transmission from mother to infant.

There was an enormous amount of controversy about that study at the start. There were-- Meetings were disrupted and stopped by protests and so forth. But ultimately what swung the study was community stepping up and saying, "This needs to be done." And particularly the community of women most likely to be the participants in that study.

More recently, we have dealt with a thalidomide trial, and inclusion of women in a thalidomide trial, women of childbearing age in a trial of thalidomide for aphthous ulcers, which is a complication of HIV infection.

I alluded a little bit ago, in the first

session this morning, to a more recent community consultation on this business of creating immortalized cell lines from a prospectively followed cohort of individuals. That sort of seemed--

When the idea came up, it was a sort of a scientific nobrainer. I am not sure that is the right phrase but, you know, it was obvious it was the right thing to do from a purely scientific point. It was--

It came up at exactly the same time as Dolly the sheep and, you know, there was all this-- There was I think some concerns on some people's part that the difference between creating an immortalized cell line and cloning, and all that--

What we did was go to the community advisory boards and the Multicenter AIDS Cohort Study and talk with them about it, and got a lot of reassurance that, yes, that was the right thing to do. It just felt good.

And I think that is a different kind of a model for going back retrospectively, for going back and getting consultation on an issue that is problematic and difficult, but doing it on the material that was collected retrospectively from a fraction of the cohort that the material was collected from.

I think it is workable, and that particular

case may be a little more germane to some of the discussion that we have had here this morning.

There are a lot of pitfalls. It is work. It is uneven. There is-- There are concerns now I think that many people have that we have created professional activists. We have created an activist industry in AIDS that now comes with its own agenda and its own set of politics which are somewhat removed from the grass roots, if you will.

I am not sure that that is an inevitable-- I am not sure that that is accurate. I don't know. And I am not sure that it is-- It certainly is not inevitable.

The other pitfalls--what has been talked about this morning--what is community? Obviously in HIV disease we have dealt with ethnic communities and risk communities and so forth. But even within the same city there is ACT UP San Francisco, and ACT UP Golden Gate, and they are basically at their throats most of the time with vehement disagreements.

I think-- What are some of the lessons that might be useful? I think I can easily envision a model where community consultation is very helpful in allowing you to take the leaps of faith, if you will, that Zeke talked about this morning, where you can't-- I don't know

that you-- I don't know that you can go and get consent.

But you certainly can go and get either consensus or a very good feeling for whether an issue is problematic or not by consulting with the community or, more accurately maybe, or better or even more optimal is the ideal of trying to discuss with community in partnership. I think consultation implies, may have an implication that is a little more paternalistic than is perhaps ideal.

The second lesson is that you can't please all the people all the time. And there is going to be disagreement, and this is a little messy, but you can certainly get a good flavor for what is going on.

And then the third thing I think is that community, whatever you do, it has to be linked in some way to the research. It has to be people who have a stake in the research and ideally you would like it to be participants in the studies.

We have actually had systems evolve that that is not the case and they are not directly stakeholders, if you will; they are not directly from the community, but they call themselves community and there are problems there. There are perhaps other things that might come up.

Bernie's final question was will such input be

possible when a community is not informed or organized or active? I think, yes, very definitely yes. It is very possible. It is very achievable and can be done. It might be harder.

We have had a little bit of flavor of that in trying to organize community input around vaccine research where the prevention constituency is not nearly as well organized as the treatment constituency, not just in AIDS but everywhere in our world.

On the other hand, it might be easier to do if you didn't have the dynamic of confrontation or mistrust as such a prominent feature, so I am not really sure which way it might go.

But those are some comments off the top of my head.

DR. LO: Okay.

DR. KILLEN: Thanks for the opportunity to offer them.

DR. LO: Are there questions?

DR. EMANUEL: I have a questions and follow up.

One is you talked about a problem which we have been confronting and banging our heads with, which is what happens when you have a lot of different groups? Who

is the legitimate political leadership you go to in a community? And what do you do when you have disagreement, as you suggested there is in a variety of spots?

And I think this is--I might preface my question by saying, in some sense--I think this is somewhat separate because it goes to a lot of the details of the processes for community deliberation, consultation, consent--whatever we are going to end up calling it--and those may be different things actually.

DR. KILLEN: It is hard. We have lots of different groups in AIDS and HIV. You have to make an effort to include them. You have to make an outreach kind of an effort to include them.

If you went over to the ACTG meeting this morning, I think you would see, among the community participants, you would see a conscious effort to be inclusive not in the sort of Noah's Ark way that committees, you know, two of this and two of that, and federal advisory committee sort of law sort of approach, but much more--

One of the things that we did was actually sort of charge the community people. And they embraced this charge so it wasn't like, "You do it," but said, "Be inclusive, find people, go out and recruit other

communities." And so it is not-- You ask the community for help in defining the relevant community and you ask them for help in recruiting it.

It takes a lot of work. It is a lot of work. When there is disagreement, you deal with disagreement like you deal with disagreement in science, or any other field; you do your best to come to some conclusions about what is the right answer. You have in place a mechanism for making the decisions.

And I think people usually respect, if they have had-- I think the big thing is that people respect a decision that they feel like they have had an opportunity to provide their input into it. If there is a well-defined process for that input being gotten; that that is the real issue.

The disagreement happens in everything you do and I don't think-- I don't see it as any different fundamentally. The community is not right all the time. That is the important point. The scientists are not right all the time.

DR. EMANUEL: I think I would second that. I think, to some extent, we are constantly being confronted by the question of, you know, what if there is not a unanimity or consensus? Well--

DR. KILLEN: There won't be.

DR. EMANUEL: --you know, in our political system, we don't have it all the time and it doesn't grind to halt. I mean, we have a system for dealing with it.

(Laughter.)

DR. EMANUEL: Well, speaking loosely here in Washington. I think it is a bogeyman. One should not expect unanimity. That is the not the standard.

DR. KILLEN: It will not be.

DR. LO: Tom?

DR. MURRAY: This is terrific, John. Thank you. It really helps ground me in what I think is probably the richest experience we have in, as far as I know, in human subjects research and trying to involve communities. And I am struck with admiration and gratitude.

But I am also struck with the disanalogies to our situation. And let me just list some of them and see if you or other members of the commission can help me think through how we can apply some of these things that you have learned.

You have an active and informed community. And a sophisticated community has become increasingly sophisticated about the research that is to be done.

Furthermore, you have a kind of natural, if you will, sanction or power on the community's part; that is, they can simply decline to enroll in one of these clinical trials. Right?

DR. KILLEN: Uh-huh.

DR. MURRAY: So it flows pretty well. If the community leadership says, "This stinks," the word gets out to the community that is sophisticated and well networked and the word is, "Don't participate in this trial," and people don't participate in the trial.

With one exception that I can think of, namely family pedigree studies where you may go back repeatedly to families who then may become sophisticated about interacting with researchers, with that aside--and that may well be identifiable in all cases anyway--that those things I think are untrue, by and large, of the cases we have been thinking about.

Where you are dealing with tissue samples and they have been collected decades beforehand, where they are being anonymized, where it may be that the community of interest, which may be difficult to define in the first place, has sort of little sophistication and little continued interaction with researchers and, in fact, no good way to--no sort of natural sanction--no way to say,

"We refuse to enroll." Here are the issues. That we give the community a kind of veto over it.

Now, I want to figure out how to make all the disanalogies go away, but I have to-- We have to--

DR. KILLEN: I think, to the extent that there is an AIDS community, which there isn't, I think it is-- but there are a lot of them, in fact--it is probably also not a valid generalization that the community is well informed; that, you know, that-- What we saw--

Let me answer it a different way. I mean, what happened was that the community that got this ball rolling was the gay white men. Early on in the epidemic, other communities were not interested, they were very poorly informed about or, maybe more accurately, they had a completely different set of priorities than research.

Their priorities--the minority community; the African-American female community's main issue--was access to health care, and all other issues were basically, you know, not germane.

I think it has required education to raise the level of the community, but you can do it. So I don't accept the fact that the AIDS community is informed and active. It is partly. It is a lot more informed-- I am sorry. It is a lot more informed than it was some time

ago. I think it is not a good generalization.

DR. MURRAY: You understand--

(Simultaneous discussion.)

DR. KILLEN: And it requires education and outreach.

DR. MURRAY: You understand I am glad to have you show me that my concerns are not-- And I think you are right. I guess what I had in mind were those people who tend now to be brought into your meeting; they have gotten pretty sophisticated about how research works, I assume.

DR. KILLEN: Yes. Yes. That has been one of the huge values.

DR. MURRAY: That could also happen in these tissues, couldn't it?

DR. KILLEN: Absolutely. Absolutely. It might not be the people who contributed the material, but it could be people of a similar ilk who could provide advice, assurance, tell you, "Yes, that makes a lot of sense. If I had donated that, I would really want to be a part of-- I would want that study to go on," or, "I want that information now."

DR. EMANUEL: Maybe the active verb there-- gotten informed--is the right issue. That they didn't

necessary start out, but the process in part helped us.

DR. KILLEN: Yes. Even, you know, even the starter community had to get informed. And then the active involving them in the process is what has created the informed community.

DR. LO: Carol, then Trish.

DR. GREIDER: My question was answered.

MS. BACKLAR: Isn't that a little bit of concern. There was a sentence you had about selling studies in the community. I am a little concerned about that. Perhaps a conflict of interest when one is selling the work that one is doing.

DR. KILLEN: I meant that. I don't know how that was heard.

(Laughter.)

DR. KILLEN: I meant that in the sense of helping recruitment.

MS. BACKLAR: But I am also a little-- I understand, in a sense, this is a kind of special community who were very eager to be recruited. You also made that point.

DR. KILLEN: I don't think that that is necessarily the case.

MS. BACKLAR: It is not?

DR. KILLEN: I think that most of the communities who have been involved in HIV research, on the contrary, are communities that traditionally have been disenfranchised from the health care system and the scientific establishment, so the process--

What I meant to say was that the process of educating representatives of the community, about what the research is about and what it is trying to accomplish and how it is going to do it, has been extremely valuable in opening up what is going on and helping the studies get done.

The information exchange from peers, in this case, is extraordinarily important. When you are reaching into a community where there is mistrust, peers have vastly more credibility than the scientists who you don't trust, and that is really all I was trying to say.

The creating mechanisms of outreach to help the research get done is extremely valuable when you are beginning with a dynamic of mistrust, but what it means is that you have had to educate people to become part of the process.

Am I addressing--

MS. BACKLAR: Right. But I am also thinking about the fact that many people in this group may have

felt that they would get better care in a research protocol--

DR. KILLEN: I am sure.

MS. BACKLAR: --than they would have outside of a research protocol, and that is something that we are quite concerned with in research generally.

And Ruth Faden's(?) committee certainly pointed that out; the therapeutic misconception.

So that there are some dangers that, some of the words you spoke alerted me to, that one would have to consider when one is educating a community in terms of research.

DR. KILLEN: Yes. I think I don't see it so much as sort of educating the activists to go out and be recruiters as much as the fact that you have involved them in the process, up front and all the way through, makes them valuable participants and makes the process of getting the research that you have designed with their help done more quickly.

Are you co-opting people? Yes. To some extent. But that is not a bad thing necessarily.

DR. LO: Larry, then Steve.

DR. MIIKE: I guess this is more directed to the people on our panel who are knowledgeable about

research.

How representative can this process be? Are we-- When we are looking-- What we are talking about is a sustained research effort in our community, however one defines it. How representative of that is this in the area that we are looking at? Are we dealing with one-shot deals, or are we dealing with sort of a whole research agenda around a particular community?

DR. EMANUEL: I think it much depends upon the research questions. But let us just focus in on-- I mean, the BRCA-1 case is, you know, you may go into it, or start out thinking it is a one-shot deal, but in fact the point is, if you identify it within a community, it is unlikely to be a one-shot deal. Right? It is unlikely--

I mean, one of the I think retorts to Tom's question is usually these kinds of studies I think, especially if they are positive, end up being part of a larger research agenda which inevitably involves going back to that community and working with them over all sorts of issues that spin out of the research.

I mean, I think, you know, when we think about the relevant communities, yes, it is definitely possible that some of the research could be a one-shot agenda, which would make all this effort necessary to community

building seem very inefficient, very much of a waste.

On the other hand, if it is part of a bigger research question, where a positive finding in the community means that you are going to be involved with them over a prolonged period of time, you know, this may just be the start.

DR. GREIDER: But that is not necessarily the case, right?

I am a researcher sitting at University X and I am just interested in a particular gene and I want to get, you know, 100,000 people and test them for that, and then I am not interested in following up on the community.

DR. EMANUEL: Right.

DR. GREIDER: Does that mean that I then am drawn into having to be involved in that community in an ongoing process? I mean, it is-- One question, I think--

DR. MIIKE: Because it is the ongoing process that I think has been what has been worthwhile. I mean, you say that they have gotten more sophisticated, you have gotten more involvement as time goes through so, yes, and I am looking at that versus informed consent or participation.

I don't see how you can get informed consent if it is-- Especially-- Even in a group such as yours, I

don't think you could get informed consent in the early stages because it was more a question about just learning about what the process was.

Does that help?

DR. KILLEN: Oh, I am not sure I understand.

DR. MIIKE: Well, I don't see how one can get informed consent in the front-end of a process where, as time goes by, you get more and more knowledgeable about the whole research enterprise around the question, so it is more like an introduction into the issue at the beginning than truly knowing what is going on and giving informed consent, however one defines a community.

DR. KILLEN: Yes. I don't think that I would portray most of what is going on here as informed consent nearly as much as--

DR. MIIKE: Well, that was my point.

DR. KILLEN: --consultation. And consultation and--

DR. MIIKE: Well, that is exactly my point, where what we have been talking about is the participation rather than a sort of like a yes or no kind of thing.

DR. LO: Well, I think--again, to go back to the example--I mean, it may well be, if you talked to some members, some representatives of the group from which the

sample is gathered, they would say, "Dr. Greider, we have no problems with that, you know, no problem at all; go ahead and do it," or they may say, "Although the last person had no problem with it, we think there are some things very different about your protocol that we would like to discuss further."

I think I would agree with you, Larry, that I am not sure that-- I mean, in a sense, formally, as I understand it, FDA's representatives are part of each committee and they participate fully, but they don't necessarily have--any one of them--a veto power.

I mean, their ideas are heard and sort of taken into account but, you know, there are scientists or other people in the community that also have votes and they could be out-voted.

DR. KILLEN: Yes. I mean, I really conceive of this as the participants in the study have an expertise that they bring to the table which is as valid, but no more or less valid, than the virologists and the statistician and the data manager in the planning of research. I don't know if that gets to--

DR. LO: Do you want to--

MR. HOLTZMAN: Just take Carol.

DR. GREIDER: I just want to-- You made a

statement in your discussion of your experiences. You said you have to have a mechanism in place for making a decision, and discussing the fact that there is ACT UP San Francisco and ACT UP Golden Gate, but there is going to be some disagreement within the community.

What kind of mechanism are you talking about if we are not talking about a consent?

DR. KILLEN: Well, it could be a lot of different things.

There is a process within the AIDS Clinical Trials Group that decides whether or not to go with a study or not.

One could imagine the funding, the process that is the funding of a grant to be the process of decision. You include community consultation in the input into the design, but it leads to the decision to fund the grant and do the study.

Those are just two things that pop off of the top of my head. That is what I meant.

DR. GREIDER: Because we had discussions around the table--I think what Larry was referring to--about a possible veto from the community and how you could do that, which is very different than what you characterized as input from the community leading to them

inputting into a decision-making process that then says go ahead or don't go ahead.

DR. KILLEN: Yes.

DR. GREIDER: It is a different structure than a veto from the community in some ways.

DR. KILLEN: I think, at least in our experience, when you hear a veto, for the most part when you hear a veto it is a *de facto* veto that is pretty obvious. And I don't know.

I don't-- There is something about this that I am not-- I feel like I am not connecting with in some way.

DR. LO: Jack, it may be that some people may be thinking--

REPORTER: Your microphone, please?

DR. LO: Some people may be thinking that community participation is another level of approval that you have to achieve, so that you go to the IRB, or you may have to go to the IRB, they may have to approve it.

But one model is that you then have another sort of community approval process you actually go through. And the specter that might raise for researchers is that, you know, it is just another roadblock that they have to go through--

DR. KILLEN: Yes. No. Absolutely not.

(Simultaneous discussion.)

DR. LO: --and you say that is not.

DR. KILLEN: Absolutely not. No. No. They are participants in the process. If you were doing a-- If you were doing multidisciplinary research, they would be another discipline at the table. The community discipline is another discipline at the table.

DR. GREIDER: Yes. But, again, if we take the example of BRCA-1, where, you know, I am just interested in studying mechanism of disease and now there is this community; that I am going to look in the Ashkenazi Jewish community. They aren't involved in my research in any way. It is not like they are already a participant. And so I, you know, define this group of people and it is a relatively homogeneous group where I could actually get information from.

So how am I going to go about beginning to involve them; to ask for community input into this study of genetics?

DR. KILLEN: I can only answer in a generic sense. You go to the community leaders and talk with them about the characteristics of the community and you find the best ways to reach into that community. That is a

quick answer. It may--

DR. GREIDER: So it is an additional thing?

DR. KILLEN: I am sorry?

DR. GREIDER: It is, as Bernie just characterized it, an additional-- There is the IRB approval and then there would be this community consent. So, in that case, it really is an additional--

DR. KILLEN: I think community. I don't like consent. I don't like that word because that is not how it operates. There isn't an approval veto mode. But there is--

DR. GREIDER: But consultation.

DR. KILLEN: Go back-- Let me go back to the example that we had. Just there is a repository of material from the Multicenter AIDS Cohort Study that people have contributed--every six months, cells and blood and tissues and so forth--to.

Some of the material there was being exhausted by requests for samples to do genetic research on, and the idea came about that it would make sense to create immortalized cell lines so that at least the DNA would be renewable, and we wouldn't have to worry about exhausting the valuable specimens, could save the valuable stuff for non-renewable things, et cetera.

I can easily imagine that, even if the community advisory boards were not in place, we could find a way to carry out a consultation with gay white men, which is who this cohort is all about--or gay men, not white men; gay men--that you would sit down with them, talk through what it is all about, and provide yourself with reassurance that you were doing something that made sense; that was something that these people were interested in; that they felt should happen.

But the approval process for the research should be the approval process that exists already. So the IRB does the IRB thing. But what you have is a level of input and reassurance and building of trust and faith in the scientific establishment; that it is doing good.

And that works both ways. It works for you and it works for the community.

DR. LO: Okay. A whole lot of people want to get in. Steve, Zeke, Tom, and then Bette.

MR. HOLTZMAN: When we get to filling in box 3b--okay?--at least we will be potentially composing a situation of what happens when the consultation provided by the relevant community--I didn't say consent--says, "Do not do the study." Yet there are a sufficient number of individuals who would eventually agree to participate in

the study and it would be a valid study.

Did you ever run into that kind of case and, if so, was the consultation which said, "Don't do the study," just positive, or was the individuals who consented just positive?

Alex Capron would ask that question if he were here.

DR. KILLEN: I don't know Alex Capron. I am having a hard time thinking of an example.

DR. LO: Well, there are some examples.

DR. KILLEN: There certainly have been studies prospectively designed where there has been a lot of controversy and a lot of heat. The decision was made to go ahead. In some cases the community that said no was right, and in some cases the community that said no was wrong.

But, again, the decision-making process about whether or not to do the research operates somewhat independently of this involvement as--

DR. MIIKE: What do you mean by right or wrong in that example?

DR. KILLEN: Produced useful and important information, or was a successful study. So when I said-- Is that what you mean? Does that answer--

MR. HOLTZMAN: You see, in the case of AIDS, if we are talking about a drug study, you may be able to get some objectivity there at the end by saying, "Did I or did I not get a useful drug?"

DR. KILLEN: Yes.

MR. HOLTZMAN: Whereas in the kind of study which really brought this group together on this kind of issue you are not going to have that--right?--because you are going to have a--

DR. EMANUEL: Even if you get a gene, people could see that is a mistake.

MR. HOLTZMAN: Right. I mean, we have got this fundamental problem. In an age of political correctness, one-- You could take a view where you are very suspect of a group, or a group of authority speaking for a group, saying, "Don't do that research." Right?

On the flip-side, you want to be sensitive to group concerns and that is-- I think we have run into that and--

DR. LO: Well, there is a real disanalogy here I think because what I think what has happened a couple of times in the clinical trial situation is where the ACTG has decided that a certain study or a certain research question doesn't come up high enough on their list of

priorities to be done.

But some elements of the community say, "Well, we just totally disagree," and they go off and do the study sort of on their own. And the Compound Q Study that was done in San Francisco may be an example.

But I think it is different when there is only sort of one repository, so to speak, or one repository you are thinking of going to.

And it is hard to imagine how, you know, if you have some people who make the decision to either approve the study or you don't, how the members of the community who say, "Oh, well, we disagree with what our community representative said and we eventually would like to do the study," how you would actually manage that with the tissue sample, or whatever.

DR. KILLEN: Well, I would say that just the model of consensus here I think is a good one; that it would seem to work for me at a very simplistic level.

You have consensus or you don't. You know, not a majority vote, or whatever. You have got a good, solid sense that the community agrees or doesn't.

MR. HOLTZMAN: Well, Zeke gave a real live example. In the Boston community, the Partner's Group--right?--decided to go out and seek input on whether or not

they ought to conduct the BRCA-1 and other genetic studies in the Ashkenazi women in the Boston area. And what came back was input that said, "Don't do it."

DR. KILLEN: Right.

MR. HOLTZMAN: And the hospitals decided not to do it.

DR. KILLEN: Uh-huh.

MR. HOLTZMAN: It probably had more to do with the sources of contributions than anything else, or one could ask that question. Right? Because now what about the individual investigator who says, "No. I want to do this study and there are a group of individuals who consent and say we are happy to participate in it. We don't care what the community said."

And I am just asking whether, if we are going to take your experience as a paradigm--that comes back to Tom--to what extent have you run into these situations and how were they handled?

DR. KILLEN: Somehow they seem very different to me because it sounds like you are talking about a prospective study, or a study where one group of individuals-- You could certain construct a study where a group of individuals consents to participate and you do the study with them.

But, in the first case, it sounded like you were talking about a study where individuals might participate without their explicit consent. Right?

MR. HOLTZMAN: No.

DR. KILLEN: Am I--

MR. HOLTZMAN: I didn't explain it well maybe.

DR. EMANUEL: Well, I think the example is, in Boston, they have not been able to launch a BRCA-1 study because the community won't-- You know, it has been up in arms. Now, no one knows whether that is the majority of the people. They haven't really gone out and tried to do it over the objections of, you know, very articulate members of the community.

And I guess part of Steve's question is what do you do in that situation? Or what would you-- Have you confronted such a situation where you might have some people individually who would say yes but, you know, your advisory group would say, "We don't want you to go ahead with that."

DR. KILLEN: Sure. Yes.

The ACTG 175 was a very large antiretroviral study--without going into the details--a randomized several-arm clinical trial. A large faction of the activists involved in the ACTG completed that study. They

campaigned against it. They said it was a huge waste of money and resources and better things could-- You know, all sorts of things. There were a few that supported it.

The group went ahead and did it. It turns out, in this case, that the study should have been done because it yielded incredibly important and valuable information so--

MR. HOLTZMAN: But at the time the decision was made to go ahead, in the face of that community opposition, what was the basis of the decision?

DR. KILLEN: A scientific-- A scientific decision, and a decision that it was an ethically sound study. It was the same kind of decision-making that would go on-- I don't-- You know, we don't treat this process as more than advisory or input.

DR. EMANUEL: Here is the other disanalogy. It is not clear that the results of that study were going to lead to a discrimination against the group, or potential discrimination. Right?

DR. KILLEN: Yes. I guess.

DR. EMANUEL: So, I mean, there the--

DR. GREIDER: Under 2b?

DR. EMANUEL: Right. 3b. Yes.

DR. GREIDER: Under 2b.

DR. EMANUEL: 2a probably. Right. Something like that. Whatever. To be or not to be. Right.

DR. GREIDER: 2a.

DR. EMANUEL: Which is why--I mean maybe why--we might want different kinds of standards here. You know, you might not weight the objection that much more.

Can I-- I just want to make an observation, and I think this is probably my political science training here.

I mean, consent here is-- I am at fault for using that word in introducing it.

And I think that, you know, there is a model of individual consent, which is the one we are used to in the medical community, and then there is a model of political consent, which is where the word originally started, that has many different kinds of connotations and implications.

And I think because, you know, we come from a medical background, a medical ethics background, every time we say the word consent, we think individual consent, sign on a form kind of stuff, whereas, when we talk about communities, I think the much better analogy is the political consent, where people don't seriatim go in and sign off their name; where, you know, you are looking for

something like consensus. You are not looking for unanimity. And there is a decision-making process to kind of integrate all of this stuff.

And I think--again, I believe that I am probably at fault for this--at least in the community side, when we are talking about what the community ought to do, whether we want to call it consultation or deliberation or input or consent, we need to step outside the box, and maybe these calls for using a different word on purpose, the sort of individual consent to a research protocol type model.

And I think part of the confusion I hear in the room is because of those two different kind of paradigms for the word. And I think, you know, we really do have to put the individual aside when we are talking about groups because there is just no analogy at all there, even though the words are the same.

DR. LO: As I understand Jack, what he was saying is that consent in the political sense is not what he is talking about; he is really talking about input into a process which many, many other people also participate in, so that--

DR. EMANUEL: It is political consent though, right?

DR. LO: Well, let us-- But it seems to me that is different than a model saying there are leaders in this community. We will go to them and they will either agree or disagree and, if they disagree, we don't do it.

That is very different than this model where there is a much larger group to which community members sit at the table, but there will be many things on which most people at the table agree with. There may be some where any one constituency will get out-voted. So I think, yes, the right terminology is--

Tom, and then Bette.

DR. MURRAY: Two things I think have become clearer for me but, after I speak, you will tell me whether that is true or not.

One is that, thanks to Steve's question, I think I understand that, in 3b, maybe even 2b, to the extent that people are identified and it is, therefore, prospective in the sense that they are asked for their consent to participation, even if the tissue had been collected before, that they are asked for consent to participate in it, then it seems to me that the normal procedures of IRB review for the protection of human subjects are highly appropriate.

But probably not necessarily community

consultation of the same kind. I am not sure. Because what if people said, "I want to be in the study," and the IRB says, you know, there is no particular harm to human subjects, do we want to insist that there be community consultation? That is-- To me, I see the question a bit differently now.

The second thing that Jack helped me see clearly is that I don't--speaking personally--I don't want to see an additional layer of committee work. You know, you get the IRB approval, then you get the community approval. That is probably not a good model for a variety of reasons.

A much more compelling model is to say, look, if you are doing a study that implicates community--and we will have to spell that out a little bit; what we mean by that--that there must, in order to even approach the IRB, you must have in place a process for community consultation, for the community has a place at the table, prior to submission of the protocol, much like what I understand you to be describing about the ACTG work.

That is a model that, at this point, I find very appealing.

DR. EMANUEL: I am not sure I understand that. Could you just--

DR. MURRAY: I will try.

Suppose a researcher wants to do a study on Gene X, which may be sensitive--we will put a kitchen sink case--may be very sensitive in a minority community that has experienced discrimination, that continues to experience discrimination.

Before the researcher goes to the IRB, whatever we recommend would be that that researcher must consult with the community, must engage in consultation, bring in the views of that community, make some, you know, modify the design of the study if that seems appropriate--whatever--and then go forward with a report as to how that consultation emerged. You know, the results of that consultation. And that is what goes to the IRB for approval.

DR. GREIDER: But someone has to determine whether a community is at stake here.

DR. MURRAY: Uh-huh. Yes.

DR. GREIDER: So what if the IRB says, "Look, a community is at stake. You didn't already do that." There has to be a way for them to have their consciousness raised and say, "Ah, right, there is a community at stake. I hadn't thought about that." And then go forward.

DR. MURRAY: Part of that is education and

part of that we are responsible for; to make it clear what we mean by that so that, you know, a diligent researcher will have a pretty clear idea of whether they need to take this step or not before they go to the IRB.

Part of it will be the kind of education that most of us remember; namely, we didn't do it right and we get sent back to do it again. That will happen.

DR. MIIKE: The same thing will apply to harm or no harm.

DR. MURRAY: We have to make that call. I am not prepared to make that call right now.

DR. MIIKE: No, no, no. What I mean is that it is the same thing that--

DR. MURRAY: Oh, right.

DR. MIIKE: --before you go to the IRB, the researchers must come to some conclusion whether there is harm or not.

DR. MURRAY: Right.

DR. MIIKE: So they are going to get second-guessed anyway.

DR. EMANUEL: Right. The suggestion there was--at least my suggestion--was that the IRB would have administrative decision-making. Did you stick it into the right box?

DR. MURRAY: Yes. Right. Is that any clearer now, Zeke?

DR. EMANUEL: It is clearer. I am not sure I agree. I am just thinking and cogitating about it.

MS. KRAMER: Well, I am just puzzled all together, and I throw this out as a question.

Does your model--does the AIDS model--really hold when it comes to genetic research?

I mean, when you are talking about genetic research, is a community identifiable or, if you do one piece of research and that research identifies a community that was never even thought to be involved--

I mean, look what happened, for instance, when they used the Tay-Sachs material and then, all of sudden, they came up with the BRCA-1, and then they came up with the colon stuff. You know--

DR. GREIDER: But it is the same community.

MS. KRAMER: Well, it is. I know it is the same community. But there was no-- There was no way that you would have--that they could have--anticipated that that would have come forward so, you know, I mean, to me it is just like a--

DR. EMANUEL: But I thought, Bette, we had addressed that in the following way. If your research is

going to a community. Right?

MS. KRAMER: Right.

DR. EMANUEL: If you are picking a community out because you suspect they have something--higher representations of whatever it is--then, you know, your research has already implicated.

If, on the other hand, you are taking lots of samples from whatever, you know, Guthrie cards--Guthrie cards isn't a good example--from a pathology department and you are getting some clinical data on them, sociodemographics on them, and it arises from that that, you know, people who seem to be Ashkenazi Jews pop out.

MS. KRAMER: Right.

DR. EMANUEL: You know, you didn't anticipate it. You know, that is a serendipitous finding.

I think what we are talking about in--

MS. KRAMER: Is where they are at--

DR. EMANUEL: --2 and 3 are when the research is specific, you know, *a priori*. It is identifying this community as one it wants to go after.

I mean, how could you do consultation in a process where, you know, you are looking--

MS. KRAMER: I guess--

DR. EMANUEL: --at random samples and, you

know, some sociodemographic characteristic pops out at you?

MR. HOLTZMAN: Yes. But how do you-- You took that case and you said it goes in the first box; the one you just said is that a sociodemographic characterization pops out.

But if, and only if, you had, as part of the phenotypic information, those relevant parameters so, for example, in the NHANES stuff, the guidelines they have come out with is that, except under extraordinary circumstances, they won't release to you those kinds of phenotypic information, such that you could never have that kind of serendipitous finding.

So are we really thinking about it the way you just described, Zeke?

That is; that whether it will fall into a community box is a function of you saying, "I am targeting a community," or is a function of the phenotypic characterization of the group such that it would allow it to go into a demographic--into a group--bucket?

DR. EMANUEL: I don't know all the deliberations at the NHANES group, but it seems-- I mean, part of the deliberations I think is because there is not any real clear guideline.

MR. HOLTZMAN: Yes. But--

DR. EMANUEL: Well, I understand but--

MR. HOLTZMAN: However your thinking is.

DR. EMANUEL: --some people may have a tendency to be more cautious when there aren't the guidelines.

I was thinking about it just as I stated. If you are going to-- I mean, parts of research are to find some such serendipitous findings. And I don't want to block that *a priori*. That would seem to me to be a real mistake.

MR. HOLTZMAN: No. I am not saying block it. Go ahead, Bette, I am sorry.

MS. KRAMER: No, no. No. Go on. Finish your sentence now. Finish.

MR. HOLTZMAN: No. I mean, it seems to me that if I go in to do a study--let us assume it is individually anonymized; all right?--but I am asking, with respect to the phenotypic information, that I want to know whether it is women, what is their religious background, what is their cultural background, et cetera, et cetera, and then I am going to go in and effectively do an association study with whatever is my finding against those parameters.

DR. EMANUEL: Right.

MR. HOLTZMAN: And it ain't serendipitous. Right? I went in looking for that kind of association.

DR. EMANUEL: But you wouldn't--

DR. GREIDER: You didn't know where you were going to associate it.

MR. HOLTZMAN: Okay.

DR. GREIDER: Where it associates is random.

MR. HOLTZMAN: That is fine. So--

DR. EMANUEL: But how could you have-- Fine, Steve. Let us--

MR. HOLTZMAN: No.

DR. EMANUEL: You couldn't possibly have some kind of community consultation process there because you have no idea of what the relative community is going to be.

MR. HOLTZMAN: Which community, right.

DR. EMANUEL: I mean, you would never get out of the box. You would never get the study underway there. So I don't see how that possibly could be the process, I guess would be my reaction.

DR. HOLTZMAN: Okay.

MS. KRAMER: I want to argue--

DR. LO: (Inaudible.)

MS. KRAMER: I want to shift it a little bit right. Exactly.

I guess where I am having a problem is that I don't handle to the whole notion of the discrimination. All right? I am an Ashkenazi Jew. I don't feel at all threatened by the fact that they have discovered this increased incidence of breast cancer, and maybe it is colon cancer as well. As a matter of fact, I feel as though I am the beneficiary of that.

Now it is true, if my medical insurance company starts denying me coverage, I am going to be madder than hell, and it seems to me that that is the problem we have got to fix.

But I consider that I am way ahead of the game because I know what risks are out there for me and I can conduct myself in a manner that hopefully is going to negate the greater risk. So I feel, you know, I am the beneficiary. And I don't understand the whole concept of why a group is going to be stigmatized by genetic discovery.

DR. KILLEN: I think--I mean from my perspective--you would be one of the people that I would want to have sitting at the table--

(Laughter.)

DR. KILLEN: --to have the research go forward to make that case.

DR. LO: But isn't the point that--you know, this article comes out in *The New York Times*--for someone in the press to say, "Wait a minute. You know, there are some problems here that maybe we hadn't been aware of," but it could give us pause.

It seems to me if you start to get that signal then you try and do a consultation and if most the people say what Bette just said, "Well, I don't agree with that article at all. I think that is a idiosyncratic view. Let me explain why I disagree with that."

Out of that consultation, it seems to me, you either get a sense that people are really split and there is very strong feelings on both sides, or you get the feeling that most people really agree with you and really want this research to proceed and think it is beneficial rather than stigmatizing, or the other way around.

DR. KILLEN: Or even that the nature of the misgivings that the people who are against it, even that is extremely useful information. You can be against it for reasons, for a lot of different kinds of reasons, some of which carry more weight than others.

DR. MURRAY: And some of which may affect your

design of the study.

DR. KILLEN: Right. Exactly. Yes.

DR. MURRAY: Maybe that is one of the things that we are most worried about is the possibility of walking back and getting identities, so you redouble your efforts to protect privacy and strip identifiers.

MS. KRAMER: I don't think--

DR. EMANUEL: Bette, can I just go back to your point? You said you would be madder than hell if your insurance were cancelled.

I mean, I think one of the concerns here is, in fact, is that insurance might be cancelled just on a wholesale group level, not on-- And that is *prima facie*--right?--discrimination. Okay?

So whether you personally feel empowered-- If the-- I mean, the whole point of I thought of those categories 2 and 3 was--or 3 was--if the group is going to be stigmatized or discriminated against, or potentially--I mean the word is potential harm not actual harm--that is exactly what the worry is.

You-- And I think your case actually brings up Steve's conflict in spades. Right? If you individually want to participate but the community is very fearful of this discrimination-- Maybe you have a great

insurance policy. Maybe you are independently wealthy and it is not going to affect you. Right?

But the other question is, you know, we found this increased risk for a whole series of cancers which we hadn't seen other ways and insurance companies are going to use this very effectively to re-write their underwriting policies.

I mean, isn't that discrimination?

MS. KRAMER: But, Zeke, is the answer to that then to allow some community to impede the research, or is the issue to make public policy such that the insurance companies can't discriminate?

I mean, I just think, you know, by the time the whole genetic library is devised and divulged, we are all going to be parts of lots of communities that are going to be vulnerable probably.

DR. LO: Let us go to Larry and Jack then. I think Tom wants to say something.

I think one of the things that has come out of the AIDS community consultation process is that, when an issue is raised in just those terms, the solution has not been to stop the research; it has been to say, "Let us try and do the research and let us independently try and put pressure on insurers and employers not to discrimination."

And I think the activist communities have been very, very helpful in those terms saying, "We have identified an issue; the way to solve it isn't to turn off the research, but it is to sort of involve the community in other ways to call attention to this very real problem of discrimination that some people are feeling."

Larry?

DR. MIIKE: Yes. There was a point Bette just made--one of the points I was going to make--which is that it is an inappropriate remedy at the wrong place, if you do--

MS. KRAMER: What is? I am sorry.

DR. MIIKE: I agree with you in the sense that you don't, you know, the research end is not the place to try to deal with the discrimination.

MS. KRAMER: Of course not.

DR. MIIKE: But I guess the way I would deal with this whole issue about what are we talking about with community versus individual, if the individual objects, we don't go and ask them, "Why are you objecting?" If they object, we just don't do anything anymore.

I mean, you know, like I can say it is because, "My moon is in the second house on that particular day," and you are not going to ask, "Is that

reasonable?"

But when we get to the--

DR. MURRAY: Well, that is a good reason. What would be a bad reason?

(Laughter.)

DR. MIIKE: But when we get to the community side, we are all sort of saying, "Yes, but we are not going to take any old reason; we are trying to delve into the reasons for it." So, to me, that is why the informed consent stuff on the community side breaks down.

And I think we are all agreed that we are not dealing with informed consent in that particular sense any more--right?--and we are moving toward a consultation model.

But, again, when we get to our final recommendations, I still am sort of struggling with this issue that we have been discussing--sometimes tangentially; sometimes direct on--which is how common is that situation where you have enough time to build a momentum for the consultation process versus the one-shot deals?

And are we going to be able to come up with some recommendations again that deal with both, or are we consciously say, in one area, there is not much concern on

that side, and makes it more an accumulate process that we have to--

DR. GREIDER: I personally think that the answers that Jack gave answered some of my concerns about the one-shot deals; that there does seem to be a way that you can go out and get at least some consultation with the community, even on a one-shot deal.

DR. MIIKE: But is that-- However imprecisely defined the AIDS community is, it is a community. And in these other areas I have a hard time identifying communities.

DR. KILLEN: But it wasn't a community-- But it wasn't a community when we started. You know? We found ways to reach into it and it is a new community all the time.

DR. MIIKE: But how did you start? You started up with the people who came out forward and complained and were activists. You didn't go out and look at the ones who were not complaining and not activists.

DR. KILLEN: Yes, we did. Actually, we did. Because many of us were concerned that we were hearing a very biased sample of community. So we did, actually, in fact, go out and say, "We need to broaden. We need a bigger net," if you will. How do we-- We did.

MS. KRAMER: But, you know, maybe the lesson to be learned from that is that community arose and identified itself because of its vulnerability, and they became activists on their own behalf because of that vulnerability. And in their activism, they have certainly advanced. They have advanced the treatment of that whole disease.

I mean, their activism has been very constructive for that community. Right?

DR. KILLEN: Yes.

MS. KRAMER: Tremendously so.

DR. GREIDER: But you are thinking about the first community that started it as--

MS. KRAMER: Pardon?

DR. GREIDER: The community that got the ball rolling. But what I hear Jack saying is that there were a bunch of other communities that weren't activists to begin with. That AIDS is not just gay men. There are a number of other communities that are involved that weren't activists. And he said it is possible to consult.

DR. KILLEN: And I think that the-- You know, we have sort of two parallel efforts going on. We have the therapeutics research program. We also have a huge vaccine research and development program, which is a

totally different community, if you will. It is a community at risk of becoming infected and--

DR. LO: Injection drug users in the inner city?

DR. KILLEN: Yes. Yes. And it is a completely different set of people. It is a community where what you are trying to mobilize is interest around prevention, and traditionally that is not a thing that our society pays any attention to.

And we have found ways to reach into that community. It is different. It is a very different dynamic. It is not an activist dynamic. It is not a beating down the door kind of adversarial relationship at all.

On the contrary, it is-- Well, there is a totally different set of things going on. So maybe that is actually a better model for most conditions that you are thinking about than the therapeutics one.

But what we have done is take the lessons that we learned in therapeutics and tried to apply them in this other very different setting.

MS. BACKLAR: Can you describe that in greater detail?

DR. KILLEN: Yes. What we are going to be

doing in vaccine trials is trying to recruit an uninfected population that is at some risk of infection and studying whether or not a vaccine protects them from infection. They will have to be followed over long periods of time.

There are all kinds of very interesting and fascinating discrimination problems that those people face. Just coming to a clinic that has AIDS in its name is problematic. People who participate in a vaccine study very well might test antibody-positive so that, on a causal screening, they would appear to be infected with all the ramifications that that might have for them as individuals.

And actually, in some of the earlier studies, we had relationships break up. We had people lose houses, lose housing. We had insurance cancelled for individuals who stuck out their arm and said, "I want to be a volunteer in this study."

So that whole dynamic is a completely different population, a different community that we are trying to reach into to understand this research process and become partners in it; help us figure out how to do research in it in ways that are fair and good and right and ethical.

MS. BACKLAR: So do you, when you are

designing a study that this, do you try to put protections in place?

DR. KILLEN: Oh, yes.

MS. BACKLAR: The kinds of harms--

DR. KILLEN: Oh, absolutely.

MS. BACKLAR: --you just described to me?

DR. KILLEN: Absolutely. Absolutely. At least until recently we had--these people had--cards that they carried that said, "I am in a research study and contact blank if I have a blood test that says..." Yes. Very definitely.

MS. BACKLAR: Yes. But, for instance, the loss of housing or the loss of jobs. You mentioned quite a few.

DR. KILLEN: Those are very isolated cases, but I think what they do is point to the problems that we need to address. And it was because we involved the community in the process of designing the studies that we were able to identify ways that the problems could be circumvented--

DR. LO: Let me just--

DR. KILLEN: --in ways that are satisfactory to the community.

MS. BACKLAR: How did you identify this

community? This was a community of people who were at some risk for the disease?

DR. KILLEN: Yes. That would vary from place to place, from circumstances to circumstances.

In Baltimore, one of the cohorts that we are working with sort of grew out of a community of injection drug users. In San Francisco, one of the groups that we are working with grew out of the gay community there. And we were able to identify people in those communities.

We just went to them and said, "What do you think we should do? Who are the people we should talk with here?" And so you do it from a local level, depending on the local circumstances.

DR. LO: I have a historical footnote, which I think is important; that, at a slightly earlier point in the epidemic, is that demographics were changing and people realized that predominant mode of infection was going to be injection drug use and sexual intercourse leads to that, rather than gay men.

A lot of people saw that the demographics were shifting. You were really talking about people of color in the inner cities. And the first attempt to get community input was to say, "Who are the leaders of that community? Let us go to them."

So people went to the churches, which are very dismal often in these communities, to elected political leaders, and they were in denial. They didn't want to talk about it. And people had meetings and the "leaders," in a political sense, weren't interested.

And I think the next wave was really much more of a grass roots level of people trying to identify community-based organizations who were providing services to people who were injection drug users, homeless, and whatever.

And I think there are some really remarkable stories of trying to sort of go and find the people who really sort of speak for those at risk, in a sense that they provide service to them and, in many cases, actually are former injection drug users themselves.

So, back to Larry's point, it isn't easy to naturally find the people you want to consult with and you may have a lot of false starts. And it takes an incredible amount of time and effort, but even in groups that aren't very well educated--the use of groups being in the positions of power--with a lot of effort I think you can really bring them in.

In that sense, there may be an analogy to some things we are talking about.

We wanted to--

DR. MURRAY: Yes. I am going to-- Thanks.

DR. LO: Oh. I just wanted to thank Jack for coming. It is very useful and we may want to come back to you at some point as our ideas crystallize and say, "How would this work in your situation and what are the analogies?" But I think this has been really helpful to get us thinking.

DR. KILLEN: Thank you for the opportunity.

DR. MURRAY: Jack, I want to add my gratitude, and to Bernie for helping to organize this.

As I recall, Paul Ramsey published *The Patient as Person* about a quarter of a century ago. And in it Ramsey developed the idea of researcher and subject as co-adventurers. At that time he saw the consent process as the key--in fact, probably just about the only--element of being co-adventurer. It would be transforming the subject from being a kind of passive exploited subject into--his phrase--co-adventurer.

What I think we are hearing today is that there is another step that has been taken and that conceivably could be taken even in our realm here--tissue samples--namely to becoming a much more genuine co-adventurer in implanting, thinking about, organizing, et

cetera, of research.

Now that would be not returning to business as usual in certain realms of research, and I am sure some researchers are going to be uncomfortable with that. And if and when we make such recommendations, we can expect to hear that.

On the other hand, we understand, from the experience that Jack related to us, that there are some advantages even to the very design of the research, but also to the general level of trust, partnership and co-adventuring that exists between subjects and researchers. And those are all things I believe are proper.

Let me tell you my proposed plan from here until noon. Another brief--real five-minute--break for those who need to take care of personal needs.

We are going to return and take up the discussion of the framework in the boxes. I think we can begin filling them in, in a more informed way, which means we will continue also to talk about community, since that is a key element in the boxes.

So far we have no one registered as wanting to give public testimony. During the break, would you please so identify yourself to Pat Norris, or another member of the commission staff, if you want to do that? We will

simply allot time before noon for that to happen. So we will begin the public testimony according to how many people want to give public testimony.

Okay. We are breaking for five minutes.

DR. GREIDER: Can I ask one quick question?

DR. MURRAY: Carol?

DR. GREIDER: Are you going to be able to stay, Jack, for this next discussion because I think it would be very valuable for that.

DR. KILLEN: Yes. Absolutely.

DR. MURRAY: Thank you. Back at 11:15 a.m.

DR. KILLEN: I wouldn't miss it.

(Whereupon, at 11:10 a.m. there was a brief recess.)

DR. MURRAY: Here is the game plan. We have one public testimony, so we will do that at 11:55 a.m.

We have now until 11:55 a.m. to talk substance, to begin filling in the boxes. We have a good background now on thinking about community consultation. We have some models on that. And let us get to work.

Zeke, do you have any inspirations on where you want us to begin filling in the boxes?

DR. EMANUEL: Well, I mean, if we--

(Inaudible.)

REPORTER: Give him a microphone.

DR. EMANUEL: The immediate thing is to do--

REPORTER: A microphone.

DR. EMANUEL: --1a and 1b--

REPORTER: A microphone.

DR. EMANUEL: --because that is the current--

REPORTER: You need a microphone.

DR. MURRAY: I got it.

DR. EMANUEL: I can't yell loud enough?

Because that is the current-- Those are the only two current boxes that exist currently. All boxes are collapsible into 1a and 1b by the common rule and, as I understand it, 1a says, I mean, if we assess IRB review, 1a, according to the common rule is, if it is going to be used in an anonymous manner, no IRB review necessary.

1b is no individual consent necessary. It is existing data.

1b, IRB review necessary and full informed consent of the individual, and no community linkage being done, so no-- I mean, they don't even recognize that category in the current standards.

And I think in these, where there is no community linkage intended, that it falls outside the purview that we are interested in.

The paradigmatic case that Steve had originally raised was looking for colon cancer genes randomly, not being worried about a particular grouping or community.

One of the examples I had circulated was the look for tumor angiogenesis factors, just going through the Brigham pathological files, of which would be the sort of 1a kind of category.

And actually I think I have here-- This is sort of the current policy outline. That is my interpretation of what the current policy is.

MR. HOLTZMAN: And the only thing we layered on top of this is, to the extent that we are going to add additional categories, that, of all instances, the IRB should make the determination as to what category the proposed protocol is in.

So even though there is no IRB involvement, in terms of approving the protocol in 1a, nevertheless they ought to say that it is a 1a protocol; therefore we don't need to--

DR. EMANUEL: I think we had labeled that previously IRB administrative review, which is does it fall into this box, or have you--researcher--made a mistake, and you needed it. It really did fall into a

different box.

Right. That would be the change from the current. This is the--

MR. HOLTZMAN: But that is a global change?

DR. EMANUEL: Right.

MR. HOLTZMAN: We are not going to put it in each box?

DR. EMANUEL: Right.

DR. MURRAY: Now, should we take them in order? Are we in agreement on 1a, which is existing samples, where there will be no individual linkage to the individual? Let us run this.

We are presuming now that there will be quite adequate stripping of identifiers, that we will have the appropriate techniques and procedures, et cetera, for that. We do have to speak to those issues.

But assuming that is all the case, do we agree that this is a case where the IRB ought to review it administratively in order to ascertain that it belongs in that category and, if it does, and if the individual's privacy is appropriately protected and there is no implication of a particular group, that it ought to then go through administrative review to be sure it is properly categorized and, if it meets the other requirements, that

that is all that we need to do.

That is too long of a sentence.

DR. GREIDER: But I agree.

(Laughter.)

DR. MURRAY: Okay. Would you explain to me what I just said?

DR. GREIDER: At the coffee break.

DR. MURRAY: Is there any discussion or disagreement about how to treat box 1a?

(No response.)

DR. MURRAY: This is going to encompass a great deal of the research that actually goes on with tissue samples.

DR. EMANUEL: Eric, you had some objection. No?

DR. MESLIN: I will defer until you continue the conversation.

DR. EMANUEL: Well, I think actually this is an important place to-- I mean, let us-- I think it might be worthwhile going through all the possibilities. Could we go back and re-consent people whose samples we want to use anonymously?

In the Brigham example, they had 104, 110--I don't remember--samples they went to, collected five to 10

years prior to the date they initiated the study. They are all to be used anonymously, in fact were used anonymously. Gotten some clinical information with them.

DR. MESLIN: The only issue I would remind the commission of is that the subject of consent, with those samples that were previously collected, is one that certainly the Genome Institute wrestled with a year and a half ago when it issued a guidance on large-scale sequencing in the construction of DNA libraries.

And the resulting NIH/DOE guidance on that subject tried to address this issue in the following ways:

First, it recognized that, while consent might not be possible from individuals, that, for purposes of those grantees satisfying their institutional requirements to either DOE or the Genome Institute, they would first have to attempt to get consent for continued use of those previous collected samples;

That an IRB would have to make a decision as to whether the protocol for using those samples was appropriate; and,

That the agency supporting the research--either DOE or NIH--would have to approve it.

Now that is a very unique case example because it is part of a set of pilot projects for large-scale

sequencing. It is also a unique example because of the collaboration between NIH and DOE on this issue.

But it is not unique in the sense that, when you have got a set of samples that were collected for purposes completely unrelated to--or potentially unrelated to--the present purpose, and when many of these libraries were constructed, large-scale sequencing wasn't an issue. The Human Genome Project wasn't even an issue. So it is not that unusual to make the tough call.

And what occurred in the guidance was the tough call that some method of attempting to identify consent process approved by an IRB would be necessary.

Now there is one caveat, and the caveat was, for purposes of the entire program, it was hoped that this situation, where reliance on existing libraries--and Carol may want to say more about this--was used, that there was every effort that new libraries, more detailed with greater depth, greater coverage, would be created as, in a sense, as quickly as possible.

So it was hoped that, although the current situation was not as satisfactory, there were certain risks in simply telling everyone that we would shut down those libraries because consent had not been obtained previously.

There was a good faith effort to develop a procedural mechanism for allowing the research to continue in the very important insertion in the interim, which was an unspecified length of time, but a hope that that period would be relatively short and that investigators, both library constructors and library users, would make every effort to get new libraries on line and quickly.

MR. HOLTZMAN: And therein lies the relevant difference, right?

DR. MESLIN: Right. Absolutely.

DR. MURRAY: Well, I am not sure that is a relevant difference.

I guess one of the things I am hearing, Eric--it is quite interesting--is what distinguishes the cases where you have existing libraries developed under circumstances of, you know, somewhat confusing consent? Minimal consent, no consent, but supposedly anonymous.

And I think what we have just-- One interpretation of what we have just assented to was that, "Well, you don't need individual consent there."

Now, I want to make an argument that the libraries we are talking about are so different in quantity of information generated about an individual--I mean, we are talking about, you know, whole genomes here--

that it really makes for a qualitative difference, but I don't know if everybody else would buy that argument.

The people that we are talking about, by the way, we are talking about the basics or the tools, collections of pieces of chromosomes that will be used in thousands of laboratories. So one individual's DNA might, in fact, be, you know, in many, many different libraries and there is an intensity to that.

Anyway, I will stop.

DR. LO: Can I ask Eric or Tom or somebody to say a little more about what the ethical objection to that is?

I mean, one I think you already addressed is that the science will be bad science and I think having NIH/DOE approval sort of, you know, takes away that concern.

Is another concern that it is really not anonymous; that you know so much about the genome that *de facto* you could identify the person or, you know, I happen to have my own copy of my genome. I can look around and say, "My God, at Northwestern University they are studying me and I didn't know about it."

Or is it the idea that, even if you don't know people are doing something to you, it is just creepy to

think that so many people are looking at your genome and I ought to have a chance to opt out?

I mean, because it would help knowing what the ethical objections were to know whether those same objections hold for studies where, you know, you are only looking at a very limited part of my DNA and, you know, you are not going to be able to identify me. It is not really me in some sense; the way my whole genome is.

DR. MESLIN: I think there are parts of each of those concerns.

And, again, remember that this discussion began about 18 or 20 months ago, which is really light-years ago, in some ways, for the way in which many of the ethical discussions about the use of DNA through the ELSI Program at the Genome Institute have progressed.

I think we were especially sensitive to the fact that this was the first time that this issue had arisen, and it arose somewhat serendipitiously. It wasn't as part of an investigation. It wasn't as part of a complaint.

It was us, in a sense, uncovering this in the course of the way that science was progressing; that there was an expectation that, based on already available samples, the Genome Project was going to be doing human

subjects research.

And in the paradigm that was operative at the time--if you are doing research on human subjects, then some effort should be made to obtain the consent of those individuals--there wasn't an awful lot of advice that could be gleaned from the common rule.

So I think it is fair to say that we were erring on the side of caution and conservatism, and for good reason, and not just simply because we were concerned about any adverse publicity, but because I think we felt legitimately concerned that, in the absence of clear guidance on whether or not these kinds of procedures could be put in place, we needed to feel comfortable--we being the Genome Institute and our counterpart at DOE--that we were acting both in the spirit and in the letter of 45 CFR 46.

Another issue--that, again, maybe Steve or Carol can comment on more effectively than I--is that we just weren't sure what the state of the science was with respect to how much information would be needed to identify individuals. And in the absence of clear and unambiguous certainty, that no one could be identified in any way, at any time. That infinitesimally small possibility was enough for us to be cautious.

Now, one can be concerned or critical or worried about whether that caution was warranted. I can say that we are now at the point where the guidance has been implemented, that the pilot projects where this large-scale sequencing is occurring are complying with the guidance, and are giving their plans for how they will carry them forward.

So I think, again, you may want to inquire with others at the Genome Institute and even others, if you think it is relevant, who have been complying with the guidance as to how onerous it is, or whether the analogy is relevant to the stored tissue debate. You might want to pursue that.

DR. MURRAY: Larry?

DR. MIIKE: Well, I look at what you have been talking about as more constrained by what were either old rules or unclear rules.

Second of all is that if we go ahead with what we were leaning toward, there is no prohibition about doing it the way that you did it anyway. We are not imposing a ceiling; I think we are imposing a floor. Right?

DR. MESLIN: I think that is right. And we also--I didn't mention it but it is probably appropriate

for the record--that this was all undertaken in consultation with OPRR, so they were aware of the guidance and, in the course of their deliberations, they have offered advice to other NIH institutes in this area.

MR. HOLTZMAN: Can we get into the facts of this case to see how relevant or irrelevant they are to stored tissues. I mean--

DR. GREIDER: I just wanted to ask-- I mean, there was one point that I wanted to make and that, is if we are really talking about box 1a, and we are talking about putting in place a robust way to anonymize something, and you believe in that mechanism that we say we are going to put in place, then this case falls out because I think this is a case of thinking that it is not truly anonymous.

So it is an exception; something that would go through that. So if we are talking about making a policy, and we believe that we can put something in place which is robust to make it anonymous, then I think that this case does not pertain.

MS. KRAMER: Are you saying that would be the IRB administrative review?

DR. GREIDER: No. That is this double-blind study where the researcher-- It really is anonymous. The

mechanism by which the researcher doesn't know the person and can't walk back.

MS. KRAMER: No. But you are saying this case would not be anonymous.

DR. GREIDER: That it would be anonymous. It would be in box 1a.

DR. LO: That--

DR. GREIDER: Oh, I am saying that--

MS. KRAMER: Eric's case would be an exception you said?

DR. GREIDER: I would say that would be a case where you wanted it to be anonymous, but you didn't really believe in the mechanism that anonymized it.

MS. KRAMER: So, therefore, the safety net would be that the IRB administrative review would catch it and say it doesn't probably belong in 1a.

DR. GREIDER: No. I am saying we should put in place a robust mechanism to anonymize things, and that we have to believe in that mechanism.

I mean, in our whole-- Everything we do is going to rely on us believing that we have a mechanism--

(Simultaneous discussion.)

MS. KRAMER: Yes. I thought you were saying that, even with such a robust mechanism, that this would

be--

DR. GREIDER: I am saying that they--

MS. KRAMER: We would be able to think that this particular case would be identifiable.

DR. GREIDER: That if I were in their situation, I would say that, because I don't believe that it could be anonymizable, then I am going to add this extra protection. That is how I would read the case the you just said; an extra added protection.

MR. HOLTZMAN: So-- So--

DR. GREIDER: But we can't put that as a policy for everything we are going to do--

MS. KRAMER: No.

DR. GREIDER: --or we are never going to believe in our own system of anonymizing things.

MR. HOLTZMAN: You can believe in your system.

DR. GREIDER: Yes.

MR. HOLTZMAN: But it could be the nature of the case of the information you are ascertaining about the sample; that it is so deep, so robust, so wide that it can't, by its nature, be anonymized once that information and, therefore, your IRB would say--

DR. EMANUEL: It is identifiable.

MR. HOLTZMAN: --it is identifiable. Right.

DR. GREIDER: Okay. Do we believe that that is the case here? I guess that I what I am saying.

MR. HOLTZMAN: Well, in this particular case, it has had less to do with the fact that I think that you were going to, at the end of the day, have the whole genome, so much as that they knew the six grad students who donated their white cells.

DR. GREIDER: So in that case it is really is identifiable.

MR. HOLTZMAN: Right? Bottom line.

DR. MURRAY: Well, I am told it was on grad students.

MR. EMANUEL: It wasn't that many.

MR. HOLTZMAN: Right. So that is why I think this is, you know, this case is--

DR. EMANUEL: It is relevant.

MR. HOLTZMAN: --is off point, right, in that it--

DR. EMANUEL: But there is a general point.

MR. HOLTZMAN: There is a general point, but it is a different point--all right?--and so what we have here is a case where we knew the people who actually contributed the DNA, number one, and, number two, you could say we are going to go get new DNA. All right?

It is not the case that you can recreate the whole archive of samples. All right? And we are postulating that we are anonymizing it. Okay?

So I think the only thing this raises--again, is this point--is, is there research which, for all the anonymization in the world, will be so deeply revelatory of the subject that it will lead you back to the subject? And when the day comes that we all carry our DNA sequence on a diskette--

DR. GREIDER: Then the answer is yes.

MR. HOLTZMAN: --all right?--and someone publishes a sequence--right?--with sufficiently long stretching, you know the answer better that I; that you will be able to say, "That is from so and so." Where you plug in your diskette and say, "You know, that is me."

DR. GREIDER: But who else--yes--I mean, who else has that information? Right? Is it--

MR. HOLTZMAN: You don't know.

DR. GREIDER: If it--

DR. : The government.

DR. GREIDER: That is right.

DR. EMANUEL: I only--

DR. GREIDER: It is only known if you know it. If you are carrying your DNA around with you and you know

that this person published it and it is your gene, then it is still anonymous.

DR. EMANUEL: Let me--

DR. GREIDER: It isn't until other people know that it is--

DR. MURRAY: Yes. But I think this is on the edge here.

DR. EMANUEL: Right. I want to raise three points.

The first point is I think we need to remember very carefully that, while it is the genetic studies that have got us started, this is by no means restricted to genetic studies. We are talking about using stored tissue for immunology. We are talking about using stored tissue for lots of other--you know, cytology--lots of other studies, as well as health records.

I mean, I think that a broad interpretation of the correct cause here is very broad, so I think sometimes the genetics is relevant; sometimes it leads us astray because I would think, at least certainly up until 1997, the vast majority of studies are not genetic studies that we are dealing with.

DR. GREIDER: Uhhhhhhh.

DR. EMANUEL: Second, I think-- Well, I may

be wrong there.

DR. GREIDER: 1985.

DR. EMANUEL: Okay. All right.

I think Eric raises an important point for us to think about. My own view is it doesn't change the substance of the decision, and that is how are we going to justify this? Now, I think that there are, I would say, three possible justifications.

One--

DR. GREIDER: Justify what?

DR. LO: Why we are not going back and consenting.

DR. EMANUEL: Right. Why we are not going back and consenting.

One, I think, you know, draws on the I think historical issue, which is historically we haven't gone back, and we have not found it necessary to go back. The interpretation of the common rule is that you don't go back.

Second is I think--these are progressively getting better, I hope--the second is a somewhat practical issue, which is that, you know, we have discovered that there are in excess of probably hundreds of millions, a 100 million samples accruing at greater than five million

a year, and there is a practical problem of going back and, unless we are going to re-write lots of rules for dead people, et cetera, there is a huge potential cost.

Third, I think that there are some deep philosophical issues at stake here.

Now are you getting satisfied, Eric? Your ears pick up?

One is I think, you know, we shouldn't dismiss or minimize advancement of scientific knowledge as a valuable item; that we here, and that the United States people and government, are constantly supporting; that they want more information and view it as a valuable good.

Second is the I think the sense that, if we really do ensure that the tissue is being used in an anonymous manner, that there is a sense that this is not, does not remain something of the individual. It is not theirs. And they don't view it as theirs. They don't behave as if they view it as theirs.

That this has entered, in some sense, a realm of a common good. People don't go back and reclaim their tissue. They don't want their slides unless it is really to check for a second opinion, and things like that.

And the third thing I think, if we really do have it anonymous, the sense of harm that is going to

accrue back to the individual is vanishingly small.

And, you know, I think there we get into the balance of what happens if we get the serendipitous information and want to reveal it where, ironically to do that, I think we raise the potential level for harm higher because of potential breaches of that where it is not appropriate.

Now I, by no means, want to suggest or imply that that is a comprehensive delineation of ethical reasons, but I think it is a list of ethical reasons that we have been talking about. And maybe there are more that will sway people different ways.

Again, my own sense here increasingly is constantly that we are in this box of you have got to have individual consent until you can, you know, move out. And I am not sure it is very helpful of applicable in this case.

DR. MURRAY: So that would--

DR. EMANUEL: So that would be some of my reasons for adopting the policy we have.

DR. MURRAY: I think this is-- Thank you. That was an excellent discussion, Zeke.

And I am assuming all along that you agree with some earlier stipulations I made about if people

objected to these in research, you would honor that. Right?

DR. EMANUEL: Oh, absolutely.

DR. MURRAY: Yes. And we would expect researchers to exercise something like due diligence in ascertaining whether or not people had objected and, if they hadn't objected, then it is okay if it is used in an anonymous fashion.

I think we have filled in a box, folks. Congratulations.

And now it is time to hear Mark Sobel give public testimony for this morning. Thank you, Mark.

DR. EMANUEL: But we have only got one box.

STATEMENTS BY THE PUBLIC

DR. MARK SOBEL

CHIEF OF MOLECULAR PATHOLOGY SECTION

NATIONAL CANCER INSTITUTE

DR. SOBEL: Well, I would like to take just a minute of your time to urge you to consider the implications of your definition of community.

It seems to me, after listening to the discussion this morning, that your definitions are very blurred. And you might have very good intentions to just have some consent and advice involved, but just remember

that whatever recommendations you make will eventually get written into some codified regulation and, as a employee of the federal government, I can tell you that the impact of that can be quite severe.

So if you are not careful in your definition of community, and especially in terms of defining disease as a community group, I could certainly see where you basically will not have any distinction between 1a, 1b and 1c, and that-- Oh, I am sorry. 1a, 2a and 3a.

That, in fact, almost everything that we are talking about could eventually be defined as some community group. And there will be implications for that.

The other issue I would like to bring up. There was a discussion about decisionally-impaired and perhaps included in that might be pediatric samples and, again, I would urge you to think of the implications of that because you don't want to put roadblocks into doing research on the health of the children of this nation that would impact on the good of the nation, so you want to--

There are special informed consent procedures right now in place for research subjects that are children, but when tissue blocks are derived from patient samples who are children, think of the implications of that in terms of how research can proceed on pediatric

samples.

DR. MURRAY: Are there any-- Mark, would you, for the record, state your name and affiliation?

DR. SOBEL: Mark Sobel, Chief of Molecular Pathology Section, National Cancer Institute.

DR. MURRAY: Thanks very much. I requested that be done. There may be a question or two for you.

MR. HOLTZMAN: Yes. Mark?

DR. MURRAY: I am sorry. We are going to make you-- This is aerobic testimony. You are going to have to keep going back and forth.

(Laughter.)

DR. SOBEL: I was told to limit my statement.

DR. MURRAY: You did a beautiful job.

Steve?

MR. HOLTZMAN: So, Mark, when I go in to give a surgical procedure, under current ways of doing things, I sign a consent which also includes the right to use the tissue in research.

So when my son goes in for surgery, and given that he is five and a half he doesn't sign the consent for surgery, I do.

DR. SOBEL: That is right.

MR. HOLTZMAN: Do I currently sign a consent

which also includes the use of his tissue in research as well?

DR. SOBEL: Presumably, you are signing the same consent form for your child that you are signing for yourself.

MR. HOLTZMAN: Okay.

DR. SOBEL: Under current-- Under the current system.

MR. HOLTZMAN: Okay.

DR. SOBEL: So that--

MR. HOLTZMAN: So that there is nothing you have said so far, that if we come up with a different level or type of consent for me, the adult, if I just extended it in the same way--

DR. SOBEL: Yes, but that is for the future.

MR. HOLTZMAN: --in my role as guardian.

DR. SOBEL: I am talking about the already-stored samples before your own commission report comes out.

MR. HOLTZMAN: Right. We haven't made any decision--

(Simultaneous discussion.)

DR. SOBEL: --those samples.

MR. HOLTZMAN: And we haven't made any

decisions.

DR. SOBEL: But I just wanted to bring that up just to think about that. I think, for the future, you can really work out a very nice scheme with adequate protections, but the issue here this morning has been the samples that have been collected before this report comes out.

MR. HOLTZMAN: Right. But I have-- Are you inferring that we have been suggesting there would be a distinction?

DR. SOBEL: Well, it did get raised by Pat Backlar that we should keep in mind how to handle samples from individuals who were decisionally impaired. And my question was are you going to include underage as part of that category, and what are the implications of that?

DR. MURRAY: Trish?

MS. BACKLAR: But aren't there protections already in place when you are dealing with research with children? I mean, I assume--

DR. SOBEL: Yes. But we are talking about-- No. We are not talking about interactive research here; we are talking about the use of archive samples that are already stored. And in most cases I am going to talk to right now--

Let us consider the case of the clinically obtained samples. The child comes in--not for a prospective research study--but the child comes in for surgical treatment or medical treatment of a condition and there is residual tissue left over at the end of that medical procedure that is not necessary for medical/legal reasons. Will you-- Do you want to consider that tissue as part of the general scheme here, or are you going to make a separate category for it?

I think that question got raised this morning and I just wanted to define that a little bit more carefully because you run the risk of impeding research on pediatric samples which would definitely affect progress on child health.

MS. BACKLAR: Even though that parent may have consented?

DR. SOBEL: Well, my personal view is that that would be adequate, but you raised the issue of whether that would be adequate, and I think you are going to have to consider that. And so I just wanted to get that issue right up front for you to really define a little bit better.

I would prefer that you not separate that out because the parent did give consent for the procedure, and

included in that was some implied or minimal--or whatever you want to call it--consent for general research, but I wanted to really--

You wanted to bring this issue up for each of these considerations, and I wanted to put that up front in terms of what the implications of that categorization would be.

DR. MURRAY: Thank you very much, Mark.

We have been at it, more or less, continuously for almost four and a half hours. It is time for a lunch break. We will reconvene at 1:00 p.m. I understand, thanks to the generous spiritedness of the NBAC staff, that it should be safe to leave belongings in this room while we go to lunch.

Henrietta?

MS. HYATT-KNORR: Yes. (Inaudible.)

DR. MURRAY: Oh. If you are here on business and you haven't checked out of the hotel, please do so now.

(Whereupon, at 12:00 noon, there was a luncheon recess.)

A F T E R N O O N S E S S I O N

DISCUSSION OF TISSUE SAMPLES COLLECTED POST NBAC's REPORT

SUBCOMMITTEE MEMBERS

DR. MURRAY: Welcome back from lunch. I would like to reconvene the Genetics Subcommittee meeting please.

I feel like I am one of those old Saturday morning cliff-hanger cinemas. When we left off, our hero was dangling from box 1a.

(Laughter.)

DR. MURRAY: Had we, in fact, reached fairly general agreement among the commissioners as to what the practice, so roughly what our answer is in box 1a? 1a is, just to be sure--

DR. GREIDER: Oh, it is missing.

DR. MURRAY: Oh, it is not up there anymore.

1a is where you are doing research on previously collected samples which are to be used in an anonymous manner in the research and in which there is just-- It is an individual sample with no obvious linkage to a particular group. Right?

DR. GREIDER: Yes.

DR. MURRAY: Good. Do we all agree on that? I think we do.

On 1b, where there is identification, I am willing to hazard an articulation of what I think our position is. If somebody else wants to do it, I would gladly defer.

(No response.)

DR. MURRAY: Okay. My understanding is, if research is to be done where the sample is to be used in the research in an identifiable manner, that there must be an appropriate consent in advance of that research.

Now, what that means is that, if the individual presumably is still alive and competent, it is that individual's consent. We have not put to rest the question of what to do if the individual is not competent or deceased. We may have to-- We will have to think about that.

But I think the general frame is-- If it is as I stated, I want to know if everyone agrees.

Bernie?

DR. LO: Can I ask you this. So the individual must consent to that specific research protocol? He or she may not consent to--

REPORTER: Would you use your microphone?

DR. LO: Sorry.

My question is whether the individual has to

consent to each specific protocol or whether patients or subjects can consent to a class of protocol? So could I just say, you know, that Dr. Greider and colleagues can do anything they want with my tissue, even if it is identifiable, once she has asked me?

DR. GREIDER: My opinion would be is, if you are willing to sign such a consent form, then it would be appropriate.

DR. LO: Let me--

DR. GREIDER: I mean, part of it is what was already signed--right?--since we are dealing with a previously collected sample?

DR. LO: Yes. Right.

DR. GREIDER: What is already on file as having been signed.

DR. LO: It is just a routine clinical consent.

DR. MURRAY: Clinical consent?

DR. LO: Both. They can--

DR. GREIDER: General.

DR. LO: They can-- The general consent; they can do whatever they want with my tissue after they--

DR. EMANUEL: That is not good enough I don't think.

DR. LO: But then having said that, Carol comes and I consent to her protocol and everything else that comes down or--

(Simultaneous discussion.)

DR. EMANUEL: In an identifiable manner?

DR. LO: Yes. Or would you want each specific protocol to get its own consent?

DR. GREIDER: Well, we are going to be dealing with consent forms when we talk about the samples to be collected in the future, right?

DR. MURRAY: Right.

DR. GREIDER: And I assume part of what we are going to be doing is trying to make comments on a more generalized kind of consent form, so that might be the sort of thing that we would consider then.

DR. EMANUEL: Let us take an example.

I mean, where is that 1b likely to happen? That is likely to happen I think in a family pedigree kind of study--right?--where you would want to use it in an identifiable manner.

In what sense would you be-- I mean, is there a class of research questions that you might want to give consent to? We do that now I guess. But is there-- Is it open-ended in general? I think I would sort of balk

that that would be sufficient. I guess that would be-- I mean, you might want to consent to, you know--

Say I have, you know--I don't know--fragile X syndrome and you are looking at my entire family. And I am going to consent to using this tissue--these blood cells--looking at fragile X syndrome, and a variety of genetic studies related to fragile X, or a variety of studies related to fragile X syndrome. That would be fine, as long as I--

But if you sort of said, you know, I am going to use it for any genetic test that comes down the line, and even, you know, look at the pedigree, I guess that would be-- That wouldn't satisfy me, I guess.

DR. MURRAY: Because? I agree with you but why don't we articulate our reasons here?

MR. HOLTZMAN: I disagree with you, so why?

DR. EMANUEL: In an identifiable manner, and getting full individual consent, what do you want? You want them to understand the objectives of the study. You want them to understand the benefits and the risks of the study.

And it seems to me that you can't do that for a wide range of studies, for a sort of class of studies on a finite area, you know, without having to have an

individual protocol for every, say, gene you want to extract, or every analysis of those genes or, you know, not even necessarily genes, you know, maybe functional studies.

You can better understand. You can give them a better delineation of risks, benefits and alternatives. But as for an open-ended one, I don't see how that is possible. I don't see how we are getting to the kind of protections we are interested in.

DR. MURRAY: Bette?

MS. KRAMER: Somebody passed out at our last meeting this proposed opt-out option on clinical care.

DR. EMANUEL: Yes. That was me.

MS. KRAMER: I think so.

DR. EMANUEL: You are going to hoist me on my own petard. It is very unpleasant.

(Simultaneous discussion.)

DR. MURRAY: I remember several people falling asleep at our last meeting, but nobody passing out at our last meeting.

(Laughter.)

MS. KRAMER: Anyway, Zeke, one of the things you have got at the bottom is, you know, it can be used for some types of research. Here. Do you want to pass it

over. You can take a look at it.

DR. EMANUEL: No. I remember that document.

(Laughter.)

DR. EMANUEL: No. But I believe that-- Let me clarify. That document was made for the samples to be used in an anonymous manner in clinical care settings for samples to be collected in the future.

MS. KRAMER: Okay. Fine. But why couldn't-- Why couldn't a person, assuming they were competent--they were making a competent decision--why couldn't they have the same options?

DR. EMANUEL: Well, I don't think-- I mean, I guess I will put my-- I don't think consent to anything is sufficient. And I think one level of protection that is afforded, by having it anonymous versus having it identifiable, makes that kind of open-ended and general consent possible, where I wouldn't take it as acceptable in the individual situation.

Because I think that there is a lot of-- It is very hard to delineate the risks and benefits for a very broad class of studies. And I think people may not fully appreciate that. And part of the protections we have is that, just because people consent, doesn't *per force* make the study ethical. It is just not-- That is

necessary. That may be necessary, but it is not sufficient. And I guess that is where I am coming from.

MS. KRAMER: Okay.

DR. LO: Let me sort of try to argue the other side of it; that if I am in a family where there is a sort of family history of a serious illness and I have a strong interest in seeing lots of research, including DNA studies done, it might actually be burdensome to keep having people mail me protocols and sign off on them.

So that if all the studies are pertaining to a major condition of my family, if they are all going to be reviewed by some sort of panel for both scientific merit and some sort of panel for kind of ethical concerns, and I have understood, in broad terms, what the risks are in terms of stigma, discrimination, things like that, I may want to give not a blanket consent, but at least a broad consent within certain parameters assuming other protections also are in place.

And, in fact, I may view it as an imposition to have people FAXing me and mailing me protocols to sign off on.

DR. MURRAY: Larry?

DR. MIIKE: Since we are going to deal with historic tissue samples, whether they are anonymous or

identifiable--not as where the tissue now stands but in the actual use of the research--then we should be consistent in dealing with these samples as we would for people who are being recruited into research. So to give a general consent for everything, even though--

I would back Zeke on that.

But in the current situation--and I will have to ask the researchers--if you are going to give a consent for a series of studies, and I assume that that is possible now, then you are given enough information so you sort of know what you are consenting to so that you may give a consent that you are going to be participating in a series of studies rather than one, and then come back and want it again.

So I would just-- I would say I back Zeke.

And where we just should make it consistent dealing with tissue as we do with the live human beings in these research areas. So that I would say that, if we are talking about identifiable tissues--in the research design it is identifiable tissue--I would deal with them the same way you would as a live human being, being--

And so I would support Zeke.

With the flexibility that you don't-- If you have a series of studies that you are contemplating

beforehand, that you can give consent for that. But if you are-- If the series of studies arises after one's project begins, then obviously I can't give consent for those studies that were never contemplated in the beginning in the first place.

DR. EMANUEL: I think the point you make about treating these people as if they were entering a research protocol is the right thinking. Now, in some research protocols--

I mean, let us look at the Physician's Health Study, or the Nurses Health Study, or NHANES. Right? You are giving consent to a broad series, but not an unlimited range of studies, if I understand that. I mean, I haven't looked at the consents there, so--

DR. LO: Those are not identifiable. The research is done-- Oh, I see.

DR. EMANUEL: No, no, no. But I am saying you are still-- You are sort of-- We haven't labeled those boxes, but somehow--

DR. GREIDER: Well, a, b, c, d, e.

DR. EMANUEL: Yes. Exactly. "e."

DR. MIIKE: Right.

DR. EMANUEL: That is the sort of range you are going at where it would be research to be used in an

anonymous manner.

MR. HOLTZMAN: Well, so, let me understand your position here, Zeke, with respect to research conducted in an anonymous manner, going forward. Are you saying that--

DR. EMANUEL: I will have to re-consult my-- Yes?

MR. HOLTZMAN: Are you saying that an open-ended consent would or would not be okay in that instance, or are you saying it is not okay specifically and only in the instance where the future research will be conducted in an identifiable manner?

DR. EMANUEL: Well, we are already hopping ahead.

MR. HOLTZMAN: But, but--

DR. EMANUEL: Yes, yes. No, no. In a relevant manner. I think if we are going to make an analogy, we should stick to it.

So box 1e-- I guess in my general sentiment there was-- A general consent would be okay. I guess maybe my-- Here is the difference. It is still this identifiable anonymizable.

I don't think actually a general consent in 1f, for example, is acceptable.

MR. HOLTZMAN: What? You see, I want--

DR. EMANUEL: Yes. And I guess that is where I think the difference is.

MR. HOLTZMAN: See, I would want to do some conceptual analysis on your position that goes as follows. All right? Are you suggesting that it is in the nature of the open-ended consent that it can't be informed? Okay. That is one take on what you are saying. All right.

Now, the come-back. Because why? What does it mean to be informed? Because I know what I am agreeing to, and that requires some sense of what the research would look like, what the risks and benefits entail. Okay?

There is another take on that which comes back and says, no. I, as an adult with some reasonable control of my faculties, can reasonably and in an informed manner consent to something that says do anything you want with it. I am not ready to go-- I will take the risks; I'll take the benefits. Right?

Without getting hung up in that, there is another way of interpreting what you are saying which says, okay, it is informed, even in an open-ended, but there is another strand that goes on in the consent process which has to do with protection. All right? The

protection of the subject. All right?

And that in the case of an anonymized study conducted in the future, under the general consent, if it is conducted in an anonymized fashion, even though one couldn't have consented in full knowledge because you couldn't have known, nevertheless the protection of the anonymization is in place, so that makes it okay. All right?

Whereas, when you are to be identified in that future study, it is not okay because the protection is dropped, and so you hang it on the issue of the protection as opposed to getting into a discussion of whether or not it was or was not informed in its very nature.

Because if you are going to hang it on that, and you are going to demand, and you are going to make a distinction between the two, then you are going to have to say why, in one instance--in one instance--though in both instances you have the absence of informed consent; in one case it is okay, in the other case it is not.

DR. EMANUEL: Well, I appreciate your analysis, Steve, but I am not sure they are all that-- I am not sure the two issues are as distinct as you make it out.

One of the reasons you are more concerned in

the identifiable case is because the potential harms are greater to that individual. That is one of the reasons we think the protections should be more substantial there. Right?

MR. HOLTZMAN: Right.

DR. EMANUEL: So I guess my feeling is, now if we focus in on 1e and f, I don't think the consent can be the same in both those boxes.

MR. HOLTZMAN: Right.

DR. EMANUEL: I would be comfortable with the consent being general in e, but not comfortable with it being general in f. And I guess I bring the analogy, move on down, and say that 1f ought to be the standard in box 1b.

DR. MURRAY: Let me make--

DR. EMANUEL: Is that clear?

DR. GREIDER: Yes.

DR. MURRAY: Let me argue--

MR. HOLTZMAN: Yes. I agree entirely actually. That is because the distinction that you are hanging it on is the potential harm.

DR. EMANUEL: Right.

MR. HOLTZMAN: And that is a standard which goes back to whether or not it is done anonymously or not.

DR. EMANUEL: Right. But the potential harm also correlates with the kind of protections you would want and the kind of protections--

MR. HOLTZMAN: Yes.

DR. EMANUEL: --in some sense, are built into the kind of consent you get.

DR. MURRAY: Let me offer a distinction and see if you think it is valid.

There is-- I think we are-- There is the consent to a particular protocol. Everybody pretty much agrees about that.

There is the consent to sort of what we have called a general consent, which would be a kind of open-ended consent to any legitimate research use of my tissues. We don't see that as problematic when the tissues are researched in an anonymous manner if, in fact, such consent was given.

The third is to a sort of series of related protocols. What I take what Carol is developing. Granted that there are no clear and bright lines between that and general consent, but I think actually, you know, we know more or less that there are research series, a series of studies done on the same tissue.

You don't go back and ask for consent for

every particular procedure you perform on the tissue. If there are a related series of protocols, that is probably, and you get consent to doing, you know, this consent to doing a series of research studies on a particular tissue in an identifiable manner, et cetera, I would think that would be perfectly acceptable.

What I would want--be inclined to do though--is put the burden of proof on the investigator to say that, "The study I want to do tomorrow, in fact, is encompassed by the consent I received from the patient last year."

And the IRB should, you know, should view it that way. If the IRB thinks, "Well, it is not at all clear that this would encompass that study," then the investigator must go back and get a re-consent.

Would that be-- Does the distinction work? Can that be a reasonable procedure?

DR. LO: Let me try and pursue that in terms of trying to find something in the middle between a general consent in the sense of do anything you want--just check it off--and a specific consent to one individual protocol.

I mean, I think there are, in the middle, are either a series of related studies or a certain type of

research that could be done. I mean, if you are going to look for one genetic marker, you know, every time someone else has another candidate marker it is really sort of a very similar study just as long as you get--whatever--a different probe or something.

And I would like to leave open the possibility that someone might say all these studies are actually sort of so closely related that it makes sense to say, you can say that not to just this one study, but other studies in the future that are roughly similar in terms of risks, benefits and alternatives.

And I think again there are other protections that you can bring into play in addition to the consent so, you know, I mentioned before either IRB approval or some ethics board.

But another thing I think is trusting an individual researcher. I mean, if I have a condition where, you know, there is one center doing all the research and I actually have, or my family has, a personal link with that institution, I may well say, "That individual, I trust them enough that I am not just participating in this one study, but a whole lot of other studies provided that it is the same person."

I-- Just to draw the analogy, I think in

clinical terms, you know, there is the same question about advanced directives. I mean, can you really be said to consent to something in the future because you don't really know what the exact risks and benefits and alternatives are?

And, granted, all the differences between research and clinical care, I think we, at least in a situation where someone is giving directives for what they are permitting you to do, in a case they know of, or are capable of consenting, we are saying that we make some trade-offs in terms of allowing research to be done, allowing clinical care to be given without the same level of specificity, but we want to be somehow guided by what the patient said before.

And, you know, again, I think whatever we decide here, we ought to make sure it is consistent with how we are going to handle samples, for example, in families where you get consent for one study and then the patient becomes incompetent before another study is done, so they are not dead and you can't use that exception, but you would like to still do the whole pedigree study, and how do you then fill in the--

I mean, Huntington's would be a great-- I mean, if the gene weren't discovered and you wanted to go

back and-- So I think we should think carefully about whether we want to leave some possibility for consenting to more than just the one specific protocol.

DR. MIIKE: Well, I don't think the argument is that it is one protocol or more; it is just a reasonableness in which you can foresee what is happening, and that person giving the consent has an idea that there are boundaries placed on what they are consenting to.

DR. MURRAY: That was actually-- I probably didn't say it. I meant to urge a kind of reasonable subject standard that, if looking at the consent-- When these identifiable studies, a reasonable--

You know, the IRB's reading of it is that a reasonable subject would have read it to include these additional studies, and I would not have a problem with going ahead with those studies without going back for expressed release then.

If the IRB is divided, or if it feels that it wouldn't be reasonable, a reasonable subject would not have had that understanding, then you need to go back. That is my proposal.

Steve?

MR. HOLTZMAN: So I am trying to understand where we are coming out, so let us use a real, live case

of a real kind of consent some of us use.

So we are undertaking, say, an asthma study, genetics of asthma, but that it is genetics is not terribly important. All right? So at level one, we describe the specific study, what will be done--all right?--in order to try to come to the genetic determinants of asthma. Then we also-- And we ask for consent for that effectively.

We then ask for consent for additional studies related to that disease that we may do in the future, the presumption being that the individuals in that have an interest in the disease and, therefore, they may very well be open to engage participating in future studies of the same ilk. All right?

And then the last level is we also then ask for the right to retain the sample and use it in any study. All right?

And, for example, so that while you are ascertaining these individuals, you also may be weighing them and getting their body mass index so, in fact, once you have identified genes potentially involved in obesity, you might want to go back out and verify them in a broader population, and you will have the BMIs for these individuals, and that is useful.

So I don't find anything conceptually problematic with offering the individuals the ability to say, "Well, I am interested in asthma only; I am not interested in that further stuff."

Now, it so happens, everything I have just described is in the context of studies which are undertaken in an anonymized fashion.

DR. EMANUEL: Yes.

MR. HOLTZMAN: All right. So my question is we could be asking for all these different-- Leave open the possibility conceptually for these different levels of consent, but we might be saying that, below a certain line, you can't ask for that if the study is to be conducted in an identifiable manner.

DR. EMANUEL: Right.

MR. HOLTZMAN: I think that is what we are saying.

DR. EMANUEL: Right. And I would draw that line between asthma studies and anything else that might come, you know, down the millennium pathway. I just-- I agree. I think that is a great example and I think you have drawn the line exactly at the right spot--

MR. HOLTZMAN: Right.

DR. EMANUEL: --which is, if you are doing it

in an identifiable manner, someone has to have a reasonable idea of what you are doing and be able to come to reasonable assessments of risks and benefits, and also how it might intersect with their personal interest.

If you are doing it in an anonymous manner, yes, I think the check-off box system, you know, to the extent that you might be able to think about it, is perfectly fine. And that I think would be the distinction between e and f there.

And all I was trying to suggest--and maybe we are now in heated agreement--is that the f move over to b, rather than e moving over to b, as the standard.

MR. HOLTZMAN: Yes.

DR. EMANUEL: Okay. So we are in agreement?

MR. HOLTZMAN: Yes.

DR. EMANUEL: Oh.

MR. HOLTZMAN: No. We are. It is just--

DR. EMANUEL: All right.

MR. HOLTZMAN: I was looking for clarification.

DR. MURRAY: f=b.

DR. LO: Let me throw a couple more issues into the hopper here.

One, it seems to me, if we are going to do

samples and call it b, d, and f--i.e., the identifiable samples--and to try to base that not on the specific consent to that protocol but from Steve's second type of consent, it seems to me there also should be a requirement of the investigator to demonstrate why you can't do the study anonymously.

So if you are going to use prior consent to something more than just that general protocol, you ought to have a special burden of explaining why you don't want to go back and get more specific consent, and why you can't do it anonymously, as sort of, you know, an extra protection.

And the other case is to go back to Tom's point about a reasonable person standard. It seems to me it is a good standard, but that "reasonable" should be interpreted not by scientists and IRB members, but should have some community input into whether it is reasonable to assume that this new protocol under consideration has the same kind of mix of benefits and burdens as was contemplated by the subject when they signed the original consent and were told about the specific protocol.

So I would have a little concern if an IRB that really was mainly composed of scientists and other university folks saying, "Oh, yes, that is reasonable that

this subject would have agreed to this other study because they consented to that one."

And I think those kinds of-- Whether that is the same thing or not is so, you know, difficult to interpret, I would want to get some community input.

DR. EMANUEL: I would like to stay away from reasonable in the standards. I have great anxiety about that for some of the reasons you have just outlined.

But it seems to me in part what you said, Bernie, is right. We should keep in mind that, in the-- Where the-- To be used in a manner where identification is possible. It is not to say that you are necessarily identifying them, for example, in a publication, or that you necessarily know, but that it is possible.

And I think the sort of paradigm case is the family pedigrees. You know, you just may have a second daughter there, but if it is possible to walk, you know, to walk backwards, that just can't be an anonymous sample, or the family just can potentially be identified.

So that-- I mean, I think in those cases there is a clear argument why you can't do it in an anonymous manner.

MR. HOLTZMAN: But I thought I heard Bernie saying that, with respect to a study to be conducted in

the future, in an identifiable manner, that one would have to go back and re-consent, even if it was of the same genre as the earlier study, unless you could show a compelling reason that you had to go back and re-consent if you were going to do it in an identifiable manner, or you had to at least show compellingly why you couldn't do it in an anonymous manner. That is what Bernie just said.

DR. LO: Yes. I mean, I think I would accept Zeke's argument that this is a pedigree study and we have to do a pedigree study, and we can't do that anonymously. That is the sort of--

DR. EMANUEL: But you wouldn't have to go necessarily back to consent if it is in the same genre, right?

MR. HOLTZMAN: Yes.

DR. LO: So I don't-- I guess what I am concerned-- I would like to leave an exception so that you don't have to go back and get specific consent for each protocol. I want to make sure that is sort of an exception that is fairly narrowly bounded rather than something that is, you know--

DR. EMANUEL: But it is not an null category--

DR. LO: Right.

DR. EMANUEL: --in your view.

DR. LO: Right. Absolutely.

DR. MURRAY: And as I understand it, there are two reasons why you want to have this exception. One is you don't want to harass subjects with constant requests for consent and, number two, you want to acknowledge that, when people did give consent, they may well have understood that it was for more than one discrete protocol and you simply want to acknowledge that.

And what we have been trying to articulate is a way of sort of figuring out when that is true. Bernie suggests, in a way, putting the burden of proof on the researcher and to say several things, one of them being why am I using identifiable versus anonymous samples?

I think that is an appropriate question to ask in all these studies. There is often a very good answer when you do an identifiable one but, I mean, it is also fully in keeping with what I understand to be best information privacy practices, which is that one should always get the minimum information needed for the task rather than getting lots of extraneous information.

Are we together on that? We might want to say something to that effect.

And also, I guess, if the investigator wants to argue that the previous consent ought to apply to this

protocol, you also place the burden of proof on the investigator.

Zeke doesn't like the reasonable subject standard. I am not sure why, but can we do a better standard, Zeke?

DR. EMANUEL: Well, I think we need a process here, which is you have to explain to an IRB--and, you know, maybe the IRB is sort of the embodiment of a reasonable subject standard--but I think I would rather have a defined process for how it goes out than to suggest a standard.

It doesn't seem to be in the same genre. It is the same disease? I am not so wild about the same kind of, you know, technical manipulation because I don't think that actually gets to the heart of what is at issue. Is it on a disease entity or a closely related entity that people had in mind, you know, are likely to have had in mind when they entered?

DR. MURRAY: Does that respond to your concern, Bernie, about IRB setting themselves up as reasonable subjects?

DR. LO: Well, I--

DR. MURRAY: Because I am a little worried about insisting now that IRBs add different members for

every protocol.

DR. LO: Well, I guess, in addition to what Zeke said, I also want to include, as a procedural criteria, that the risks and burdens are, you know, roughly speaking, the same or very similar to what the original protocol was, or at least the patient understood them.

I guess I do have concerns--it maybe intersects with what the other subcommittee is doing--that I am not convinced that IRBs, as they currently operate now, provide adequate protection, just to look at what they are being charged to do now, let alone if we are adding some extra tasks on top.

And I guess I am persuaded that, even with all the problems we have talked about this morning of obtaining sort of an outside opinion from someone who is not a member of the institution that is conducting the research, I mean, in my IRB, all the two members are, you know, they are employees, they are faculty members, or something.

And I just think it is a little bit different if you are sitting there because, you know, you are from the community.

And also I think it is not that big a deal, if

you have a protocol being sent to you, to say, even if there is no one on your committee that is an expert in this, to send it out for review to whatever--an advocacy group, or something--to say, "Does it make sense to you? Do you have any serious objections concerning this protocol to be similar enough to the other protocol, and the sort of second-level consent that should be included?"

I am just concerned that, you know, that at the IRB they get about three minutes per protocol. And, you know, they are basically, you know, is this number 18 or 17? And they can't really give-- It is very hard for them to give every protocol the attention that they might want to give under, you know, more ideal circumstances.

So that is really something that, you know, our other subcommittee is working on. But I am not-- You know, I am just cautious here.

DR. MURRAY: Well, has this discussion gotten to the point where we can go back and begin to think about boxes? We are still on 1b as far as I know. Somebody else take the track.

DR. GREIDER: But 1b=1f, so we are getting ahead.

DR. MURRAY: Yes, we may be. Yes.

DR. EMANUEL: Well, we have elaborated

something about 1e in that already.

DR. MURRAY: Okay. But can somebody help me at least--and Kathi and whoever else is going to be in charge with being our scribe--with what we are saying about 1b?

First of all, no research on identifiable samples without consent. Are we saying that?

DR. EMANUEL: Yes.

DR. MURRAY: Does everybody agree on that? And that is true of 1b and 1f. Okay.

We have elaborated some of the complexities there. I mean, is it really the same study or is it a different study? I mean, we may want to suggest a specific process and we have some of the ingredients for that. But I guess that is really the answer, isn't it?

DR. EMANUEL: Uh-huh.

DR. MURRAY: No research without appropriate consent.

DR. GREIDER: I mean, I think that it was very helpful that Steve outlined the sort of 1, 2, 3. The consent for this specific study; consent for something very closely related to this kind of study, but not the third one which is the complete anything.

DR. MURRAY: Well, that is why I used the word

appropriate. What counts as appropriate will depend on, you know, what is the understanding that we can reasonably read into--

DR. GREIDER: But having those categories outlined in that way, I think we are going to get back to them when we get to 1e--

DR. MURRAY: Well, I think--

DR. GREIDER: We discussed that those three categories were useful categories, so maybe having them go throughout the chart might be worth keeping in mind, rather than just using descriptive terms.

DR. MURRAY: Right. Okay.

DR. EMANUEL: I mean, it seems to me that qualifies as--in my mind--full, informed consent. You have a delineation of the objectives of the study, the risks and benefits of the study, the alternatives and, you know, whereas either a specific study or a class of studies. And I guess in my mind that is full, informed consent.

DR. MURRAY: Okay.

DR. LO: Are we going to-- Are we going to a surrogate consent for children and adults who lack decision-making capacity?

DR. MURRAY: Are we going to allow surrogates?

It seems-- And this is in identifiable samples?

DR. LO: Yes.

DR. MURRAY: Okay. Let me-- Let me offer an answer. Yes. Just as you would for any other research on human beings.

Trish, what do you think?

MS. BACKLAR: Yes. Yes. I agree. But I think the process-- We are thinking through very carefully about who those surrogates might be, how they might be educated, or they might know or not know, and we are also thinking of other safeguards, not simply the surrogate decision-maker.

Even in this case it may not be in the same kind of safeguards that you would want because there are differences in the kind of research that we are considering, and that is important to identify those differences.

DR. LO: Just to play devil's advocate, I mean, two things we should probably think about.

One, with regard to genetic research, what if I am the person giving consent for my parent who is decisionally impaired, for my child, what I am hoping to gain for myself may not necessarily be what is low risk for somebody else in my family, so there is at least a

potential for conflict of interest.

MS. BACKLAR: And particularly, in terms of one thinks perhaps of a child, because that may be in the future, which might be very different information that you get than you even might expect at this particular point, and when the child is an adult they may not wish to have this, or they wish more, or whatever.

DR. LO: And you can. Remember, there are concerns about whether-- Well, this isn't-- In a clinical setting, whether parents should be allowed to consent to clinical testing for genetic, you know, genetic predispositions as opposed to late-onset, as opposed to waiting for a child to reach maturity.

The second point I think we need to think of again is the empirical evidence that suggests that when, at least in the dementia setting with adults, when you ask their family members to give surrogate consent, they often do not, at least currently, or when the study was done, act according to what the patient would have wanted, or what is in the best interest of the patient.

MS. BACKLAR: Actually, there are some other studies now which negate that.

Greg Sachs(?) has a study in dementia--an interesting dementia study--in which there was an

interesting correlation between what the patient wanted and the surrogate wanted, which is another issue that we haven't dealt with here.

And that is that many of these people may be able to give assent and yet not complete informed consent, the way we identify with somebody who has complete capacity, both a child and an adult, who may have questionable capacity still may be able to have some understanding. And you wouldn't want to-- You would want to be able to get that as well as the surrogate.

DR. EMANUEL: But that is our current standard. I mean, when we talk about full, informed consent that is what we mean. Right? If you are dealing with a 14-year-old child, that is what we mean. Right? You have to get that kind of assent.

I think-- I mean, my view is these boxes, these 1b and 1f, are not really any different from what we do now.

MS. BACKLAR: But that is what I am trying to get people to say. How is it different?

DR. EMANUEL: I don't want it to be different in these boxes. In those two particular boxes, I don't think they should be different.

MS. BACKLAR: What you are talking about

though is the research is different. Is that correct? Is that what you are saying that is different? What is different then?

DR. EMANUEL: Different from what? Different from the current situation?

MS. BACKLAR: Yes.

DR. MURRAY: Nothing.

DR. EMANUEL: Nothing. The answer is nothing.

MS. BACKLAR: Okay.

DR. GREIDER: What is different is that there are 2 and 3.

DR. EMANUEL: Yes.

DR. GREIDER: We are adding extra columns on.

MS. BACKLAR: Right.

DR. GREIDER: In the one--

MR. HOLTZMAN: To the extent that one thinks the current standard--

MS. BACKLAR: But we also heard that 2 and 3 wasn't so different, not necessarily, just genetic.

MR. HOLTZMAN: From each other?

MS. BACKLAR: Right.

MR. HOLTZMAN: From each other.

To the extent-- I think to the extent that we feel the current situation could use improving, with

respect to what is sought in the way of surrogate approvals, what that process should look like, what is sought of children--all right?--whatever one comes up with there, in terms of protection of subjects, we would say would equally apply in 1b, f, and, probably by the time we are finished, 1d, for what it is worth.

But having said that, Bernie has raised the case that has come up in the context of genetics research, which I think is actually not a genetics issue--it is a more broad issue--which is when the nature of the test or the research can reveal something about the subjects which only has an implication later in life and, in such instance, can an adult either, A, approve their child's participation in such a study or, if they can, do they then have to withhold from that child the information gained in the study?

Some have advocated, you know, taking in the clinical test example, you can't get your kid, you can't consent for your kid to get a Huntington's test. Full stop. All right? That is the current position of the Huntington's community.

So when we are talking-- Again, you could say whatever is the case in general for consent; we will just say that applies here. Right? But do we have an opinion

on that, that we want to bring forward here when we are talking about what is and is not consentable?

DR. EMANUEL: I would-- My own view is we should try to pass over those things in silence. We should focus in-- We should focus in on where we are going to make our contribution, and not re-hash something where I don't think it is of the essence of what we are looking at. That would be my preference. Because it is a whole other issue which has taken a lot of other people a lot of time, and I am afraid it might side-track us.

DR. GREIDER: I mean, another way of saying it is what Larry said; is that we are looking at the floor here, not the ceiling. Right? Whatever things you are talking about would be in addition; would be more protections--

DR. EMANUEL: Certain parameters.

DR. GREIDER: --that could be added on top of what we are doing here. Right?

DR. LO: I would want to argue--at least have us think about--the contrary position, which is that, to the extent that people have concerns, whether misinformed or otherwise, about the nature of genetic testing, genetic research; that, you know, if my child gets tested and is, you know, is part of research tied with high cholesterol,

that is not as potentially stigmatizing. No one thinks it is really determinative or dispositive the way-- You know, if you really get the gene it might be.

And so I think we need to deal with all the sort of preconceptions of prejudices and assumptions that may make a difference with this kind of research compared to other kinds of research we might be doing.

If what we are saying is the floor is-- We think the current guidelines for all clinical research are fine, with regard to this particular type of clinical research, then we ought to be prepared to answer the objections that some may raise that, "Well, wait a minute; aren't there things about DNA testing on stored samples that is different than epidemiological testing or protein, you know, marker testing?"

DR. MURRAY: I guess--

DR. LO: You may be right.

DR. MURRAY: --I favor something in between passing over in complete silence and trying to deliver the definitive ground-breaking rule.

What I would say is let us lay out our basic structure, basic rules, and admit that there are certain, you know, complexities upon this, like a test for, you know, the one-year-old child for Huntington's.

And then refer to the existing literature on it and maybe not attempt to say anything new about it but say, you know, the IRBs and researchers and families ought to be aware that there are levels of complexity in this kind of case. And I think we will have a fairly finite and probably not a long list of those complexities.

Would you be--

DR. EMANUEL: Yes. I mean, to acknowledge that these things exist is absolutely essential. But reanalyzing the justification for each one of those I think would be a mistake here. That is what I meant.

DR. MURRAY: I agree with that.

MR. HOLTZMAN: But I think Bernie raises something that has been a lot on my mind, and that is we have pretty much, as a commission, every time we have taken on the subject concluded that we would like to explore the myth of the genetic exceptionalism. Right?

DR. MURRAY: Uh-huh.

MR. HOLTZMAN: And this is the first product of the Genetic Subcommittee. And I think we have to take that head-on probably because we were tasked with looking at genetic testing of samples, and we are coming back talking about testing of samples. Why have we taken that position?

And there are many implications that come out of it. One particular one is, if you think that there is something special that ought to be done in terms of consenting to test for children where the implication is later in life--all right?--that is true regardless of whether it is a genetic test.

DR. MURRAY: Absolutely.

MR. HOLTZMAN: So that is one instance.

DR. MURRAY: Yes. I agree.

MR. HOLTZMAN: We have another one which is when one talks about consenting to classes of research. So if you look at the National Breast Cancer Coalition consent, one of the classes of research they talk about is genetic research. I think what we are saying is that that is a meaningless class. That is the most strident position.

DR. EMANUEL: But I would actually-- I think, before jumping ahead, part of the outline does take into account that. And I guess I would add my voice to those I guess who are saying that, you know, we should make clear that we are dealing with the whole-- We are talking about testing, not just genetic testing, and that, in many cases, the implications are the same, and one need not-- That that distinction is not necessarily that helpful to

us.

DR. MURRAY: Yes. Good. We are--

I am going to recognize Larry.

And then I want to see if we are ready to move on to the next step. It sounds to me like we have got 1b, d, and f. Do we have different rules for them? Do we have the same rules?

DR. GREIDER: 1b, we still have the case of the dead. We haven't said anything about that yet.

DR. : The case of the dead?

DR. GREIDER: I hate to raise the issue but--

DR. MURRAY: Well, how about the living persons; 1b, d, and f. First of all, are they the same? That is number one.

DR. EMANUEL: Well, I would say I think we should hold out on d. I am much more convinced about f.

DR. MURRAY: b and f are the same?

DR. EMANUEL: Yes. Hold out on d, because I am not sure that we have--

DR. GREIDER: b=f.

DR. MURRAY: Well, okay. Explain to me why d is-- No. Using letters gets confusing.

Explain to me why samples that we got in a clinical setting, why we wouldn't ask of those samples,

when they are to be used in an identifiable fashion, why we wouldn't require that they get specific consent? I don't understand. That, I don't get. Because that is the standard we set for b and f.

MR. HOLTZMAN: And the majority of b were collected in a clinical context.

DR. MURRAY: Right, right, right.

DR. EMANUEL: All right. I will agree.

DR. MURRAY: I think we should stop the meeting right here. I am not usually that persuasive.

b, d and f, 1b, d, and f look pretty much the same to us then.

Carol raises the problem of what do you do when a subject is deceased, which--

DR. GREIDER: Pretty much only b.

MS. BACKLAR: d.

DR. GREIDER: Well, I mean, the people-- The other ones can die as well I guess.

DR. MURRAY: Yes. It is-- Yes and no. I mean, samples collected in the future may include, say, "Please contact me again." And then they are dead the next time you go to contact them. So it does and it doesn't.

MS. BACKLAR: But then they would lapse back

then into previously collected samples because--

DR. MURRAY: Well, no, because they have been collected with a more robust consent.

DR. GREIDER: Right.

DR. MURRAY: But they may want-- And we may in fact want to apply the same principle to dealing with deceased subjects in all classes. We may.

DR. GREIDER: So my proposal for the deceased subjects in 1b would be to move them to 1a.

DR. EMANUEL: As if it were anonymous?

DR. GREIDER: Uh-huh.

DR. EMANUEL: Even though it is going to be identifiable?

DR. GREIDER: No. Anonymize them.

DR. EMANUEL: No. But if you are doing a family pedigree, there is no way of anonymizing them, for example.

DR. MURRAY: Yes.

DR. EMANUEL: I guess that is the sample--

MS. KRAMER: Well, if you are doing a family pedigree, haven't you gotten consent from the other members of the family? In other words, you wouldn't be running the risk of--

DR. EMANUEL: Well, there could be holes in

that consent process. I mean, one needs to-- You know, you could have parents--right?--both of whom are dead. You could have one sister who agrees and one sister who doesn't want a test, and maybe a third sister who you have yet to contact.

MS. KRAMER: Are you able to go ahead under those circumstances?

DR. EMANUEL: Well, you are certainly able to go ahead with that sister and maybe her children.

DR. MURRAY: What is the current practice and what are the federal rules about dealing with those? Mark?

DR. SOBEL: The federal rules do not apply--

REPORTER: Would you go to a microphone, please?

DR. SOBEL: The federal rules do not apply to samples from people who are no longer living, therefore autopsy material is exempt from the current rules, as are samples that are currently in archives from people who are deceased. And, you know, you have to think of how far back you are going to go to try to track, and how you are going to figure out who is the responsible individual.

DR. MURRAY: Put it the other way. A family comes right to your hospital and says, "I know that so and

so--my father--died while, you know, in this hospital and I have been told that there may be samples. We would like to have use of them in a pedigree study that an investigator is conducting." What do you do?

DR. SOBEL: There is no rule against doing that, but I imagine that most hospitals would hesitate before automatically releasing that information, and I would think that at least some of them are going to buck that up to an IRB or some review board for approval. But technically there is no law against somebody doing that.

And usually, at least in current time, when people go into the hospital they sign a form and they designate a surrogate, and then that surrogate can be contacted or, if you are the designated proxy, then you are contacted as the responsible person.

(Simultaneous discussion.)

DR. EMANUEL: You must have had a peculiar NIH experience.

DR. SOBEL: No, actually. I am-- My sister died and she always listed me as the person to contact in case of an emergency, or she was part of the Guttman(?) Institute Study and I was listed as the person to contact should anything happen to her so, therefore, I have the authority to release her records for a study. And so I am

contacted, and have been, to give that approval. But that is a research study; that was not a clinical care.

DR. MURRAY: Thanks, Mark.

DR. SOBEL: But there is no federal rule that regulates any material from deceased individuals.

DR. MURRAY: Carol, do you feel like you have an answer or enough information on which to make some recommendations about how to deal with deceased subjects? We could just say as it is dealt with now, which is there are no rules.

DR. GREIDER: I don't have a particular issue here. I mean, I think we need to discuss it though just because we haven't discussed it, and that whole category there. If people feel comfortable with having it be--whatever you want to do in many of the categories--which is as the regulation is now.

DR. MIIKE: Wouldn't it depend on whether the research has implications for a blood relative? I mean, if it is research just on the dead person, and there is no extension of that research to the immediately family, it is not an issue.

DR. GREIDER: But of course it could be an issue because we are talking about pedigrees here, so that is going to have implications to all the relatives.

DR. MIIKE: But--no--but we are dealing with tissue samples as a generic issue.

DR. GREIDER: Yes.

DR. EMANUEL: I mean, let us just look. If you are-- If you have died and your tissue is going to be used in an anonymous manner--all right?--we don't have a problem with that. Right? I mean, we have got a system where it doesn't require a seance to get your consent.

(Laughter.)

DR. EMANUEL: 1b, you know, you are going to identify that person--

MR. HOLTZMAN: So we will have a seance.

(Laughter.)

DR. MIIKE: I was going to say only dead researchers could conduct it.

(Laughter.)

DR. GREIDER: There are some good ones.

DR. EMANUEL: But you are only going to-- I mean, the implications there are going to be for-- Right. I guess the issue is if you are dead you can't be harmed. Right? I mean, the idea is that you can't be harmed. Right?

There are no risks and no benefits to you, but someone related to you. I mean, presumably the reason for

doing it identifiable is that someone related to you could get benefits and harms.

DR. GREIDER: That is the only reason for doing identifiable research--

DR. EMANUEL: Yes. Right.

DR. GREIDER: --on a dead person? Right?

DR. EMANUEL: Right.

DR. GREIDER: There are no benefits to a dead person; to do research on them. The only people that--

DR. MIIKE: Not that we know about at this present time.

DR. GREIDER: The only people that are benefitted or harmed are the relatives.

DR. MURRAY: Right.

DR. EMANUEL: Yes.

DR. GREIDER: So that is what you are dealing with, no matter whether you are doing genetic or non-genetic, whatever you are doing.

DR. MIIKE: But when you do those studies, do you usually do it in isolation from studies on other family members? They are done usually--

DR. EMANUEL: I don't know. Not if it is going to be identifiable. I mean, the only reason to have someone as identifiable is-- I mean, in those cases, it

is usually potentially identifiable because you want to link them.

DR. MIIKE: So--yes--so you would be-- The research would also include using other subjects that are related to the dead person?

DR. EMANUEL: Right.

DR. MIIKE: Well, then, doesn't that solve the problem if you have to have the individual--

DR. EMANUEL: But you assume consent throughout the family. I mean I think, at very real times, there isn't. Not everyone agrees.

DR. MIIKE: But, what-- Wait, wait, wait. If you are starting off with a dead person's tissue, and you are going to do family pedigree studies where it must involve other family members--

DR. EMANUEL: But say one sister wants to go through with the study, but one sister doesn't. We have that case at the Dana-Farber now.

DR. MIIKE: Okay. No, no. But I am saying is that so you conduct your study with the one who consents and you don't conduct the study with the one that doesn't.

DR. GREIDER: But what do you do with the dead person?

DR. MIIKE: Well, from my point of view then,

if some members consent, then it is okay to use the dead person's tissue because you are getting some modicum of consent and you can design your study around it.

MS. KRAMER: I am going to toss a coin.

(Laughter.)

DR. LO: But there is another problem. Suppose the dead person, while alive, had said, "I don't want to be a participant in this type of research."

DR. MIIKE: Well, then they lose.

DR. GREIDER: That is clear.

DR. MURRAY: Our initial rule is that you don't use it--

(Simultaneous discussion.)

DR. MURRAY: I would say yes.

DR. EMANUEL: It tracks.

DR. MURRAY: It survives.

DR. LO: But is that different than the current federal regulation?

DR. MURRAY: Is it?

DR. LO: Now my understanding is the current federal regulation says nothing, so nothing would prevent you from doing it.

DR. SOBEL: I don't think you--(Inaudible.)

DR. MURRAY: Yes. We don't want to create a

situation in which, when you have got balky subjects, where the researcher has an initiative to knock them off in order to be able to conduct the research.

(Laughter.)

DR. SOBEL: Yes. There is a federal rule that says there is no--basically, in essence--no protection if you are deceased.

On the other hand, hospitals do not do autopsies--

DR. EMANUEL: On everybody

DR. SOBEL: --without permission.

DR. GREIDER: Right.

DR. SOBEL: And they don't have to actually ask for that permission, but they all do because they know that there would be hell to pay. And so, in fact, in practice--

DR. EMANUEL: Well, no. Wait, wait, wait.

DR. SOBEL: --the family gives, even if an individual gives permission for an autopsy to be performed, if a family member objects to that, very often there is a hesitation before proceeding.

DR. EMANUEL: But that is because the family owns, by common law, owns the body.

DR. SOBEL: Yes. But, you know--

DR. EMANUEL: That is a different story. It is not--

DR. MIIKE: Look. There are going to be a lot of cases where tissue has been collected, the daughter said, "I don't want it used for research." By the time the tissue is about to be used, that person is dead. We are still going to honor that wish.

DR. MURRAY: I would say we should honor that. I would be willing to go on the record and put it as one of our recommendations.

Yes?

MS. HANNA: I was just going to suggest maybe this is an area where staff can try and find out for you whether there is existing regulation and whether the Uniform Anatomical Gift Act has any relevance here. So we can find out.

DR. MURRAY: All right. Can we--

DR. GREIDER: But we still need to make a decision about what we think it should be, regardless of what it is.

DR. MURRAY: So this is not a dead issue.

(Laughter.)

DR. EMANUEL: I think we should put it aside and try to fill in more boxes because I don't think it is

an-- I mean, it is an important issue, but I don't think it is quantitatively and qualitatively that difficult.

DR. MURRAY: Okay.

DR. GREIDER: I guess we will come back to it.

DR. MURRAY: I am sensing a general agreement on Zeke's point. Let us go on. Let us go on.

Do we know now what we are doing in 1a?

DR. GREIDER: Yes.

DR. MURRAY: 1b, d, and f? We also know what we are doing in 1e? Do we?

MR. HOLTZMAN: What do we have going in 1e?

DR. MURRAY: And what about 1d?

DR. GREIDER: I am sorry.

MR. HOLTZMAN: What do we have--

DR. MURRAY: 1c.

DR. GREIDER: It is c and e that we have to do.

DR. MURRAY: c and e.

MR. HOLTZMAN: What do we have in 1e?

DR. LO: General consensus.

DR. GREIDER: I think we have what you said, Steve.

DR. LO: Yes.

DR. GREIDER: Your three-part--

DR. MURRAY: Well, we have--

DR. GREIDER: Your three-part consent. Specific, specific general to the disease, and anything. That is what--

MR. HOLTZMAN: And all of those can be available.

DR. GREIDER: That is what I understood us at least discussing.

MR. HOLTZMAN: Right.

DR. MURRAY: And we have actually someone with us from I think the National Action Plan on Breast Cancer and--

MR. HOLTZMAN: Then let us move on to 1c.

DR. EMANUEL: I don't think so.

DR. MURRAY: He just walked out?

DR. GREIDER: That is relevant to 1e.

MR. HOLTZMAN: No. The National Breast Cancer is relevant to 1c.

DR. GREIDER: 1c.

MR. HOLTZMAN: 1c. Not 1e. What I have described is paradigm 1e. Okay?

DR. EMANUEL: Is what I would call a general kind of consent.

MR. HOLTZMAN: Where that in--

DR. EMANUEL: With a--

MR. HOLTZMAN: --if what you are seeking is to do anonymized research that you may get informed consent to wide open anything that--

DR. EMANUEL: Correct. And that would be perfectly fine. So you would have the possibility of delineating the objectives of the research in a very broad and open-ended manner.

MR. HOLTZMAN: Right.

DR. EMANUEL: Yes. I would classify that as general consent.

MR. HOLTZMAN: Right.

DR. EMANUEL: Whereas I am not sure that we even need that for 1c, but we can talk about that.

MR. HOLTZMAN: Right. That is all that is left. All right.

DR. MURRAY: I am sorry. It sounds like a wonderful agreement was reached. I was unfortunately engaged in figuring out how to get Debbie Saslow here. What was-- Could someone--

DR. EMANUEL: Well, for box 1e, IRB review.

DR. MURRAY: Yes.

DR. EMANUEL: That is, you know, the right box and review of the research studies, and a general consent.

DR. MURRAY: Is adequate?

DR. EMANUEL: Yes.

DR. MURRAY: Yes. Do we all agree on that? And I think we can articulate the principles pretty clearly on that.

MR. HOLTZMAN: But let me just get clear. General consent is the thinnest form of consent, right?

DR. EMANUEL: Uh-huh.

MR. HOLTZMAN: So we are not advocating-- We are not advocating that, if one wants to undertake, even in an anonymized fashion, a research study, that you should go in and say to someone, "We just want to conduct some research." Right?

We would advocate that, to the extent you know the study--right?--that you articulated in detail, et cetera, et cetera, but what we are saying is that it is okay, in this context, to also seek a general consent, and that a general consent is adequate for the future conduct of research in an anonymized fashion.

DR. EMANUEL: Well, let us just look at it. You are collecting a sample in the context of research studies.

MR. HOLTZMAN: Right.

DR. EMANUEL: Okay? So you already have--

The person is enrolling for a research study. So you have an objective for the study, risks and benefits associated with that, but you can also ask for, in that context, we are going to keep the sample around for potential--

MR. HOLTZMAN: For the file and for agreement.

DR. EMANUEL: Okay. But, I mean, because it is already in the context of research, you have to get an informed consent--

MR. HOLTZMAN: For the specific.

DR. EMANUEL: --for the specific protocols.

DR. MURRAY: I think, if I understand Steve's point, we need to be explicit about that requirement.

MR. HOLTZMAN: Right.

DR. MURRAY: That it is not enough to get a vague general consent for the first use of it.

MR. HOLTZMAN: Yes.

DR. MURRAY: Okay. That is-- We just need to put that--

DR. EMANUEL: Yes. That is a very good point. Good point.

DR. MURRAY: --clearly in the report.

DR. LO: Then, to follow on to that, I mean, do we also need--want--the sort of general consent to include some discussion of potential risks and benefits

that might prove and particularly--(Inaudible.)

DR. : (Inaudible.)

DR. LO: So it is not just you can say, "Here is my really detailed thing, informed consent, for my specific protocol," and you have got one page, or the back, saying, "And, yes, Dr. Lo can do whatever else he wants in addition."

I mean, I should have to say, you know, the kind of studies we are proposing might have the following kind--

DR. MIIKE: But it is going to be done in an anonymous manner. It is the anonymous one. It is e we are looking at.

MR. HOLTZMAN: Right. But I think what Bernie is pointing to is the kind of risk that is pointed to in the National Breast Cancer consent--

DR. LO: Yes.

MR. HOLTZMAN: --where they say there are very few risks. The greatest risk is the release of information. We are proposing its use in an anonymized fashion, but there is the informational leak risk.

DR. LO: And also that we don't propose to get back to you if we find anything that might be pertinent to your health because we have done this anonymously. Right?

DR. GREIDER: I think some description of--

DR. LO: What it means to be--

DR. GREIDER: You know, we are going to have this process to anonymize things, and it is going to be a very robust process. And some very brief, easy-to-understand description of that process should be in there so that they understand what the protection is. The double-blind study, or whatever. That the information does not walk back.

DR. LO: I mean, we should, as best we can, let them know what is going to happen to their sample, or what the benefits and risks to them are.

DR. EMANUEL: Yes. But part of the point is we don't know what tests are going to come down. I mean, we can't say in specific. I mean, if we could say in specific, then we should get their consent.

DR. MIIKE: But acknowledge--

DR. GREIDER: But you can show--

DR. MIIKE: Yes. Just describe what we mean by anonymous. That is all.

DR. GREIDER: You can say what the process is that is there to protect them. You don't have to say, "Just trust us." You can say, "This is the process."

MS. BACKLAR: But you also have to be specific

that the risks are unknown. That is something that becomes clear to us. Because you just said this; that the risks are unknown. When you are getting a general consent in this way, and you are not being specific, there may be risks that you couldn't calculate.

DR. GREIDER: If it is anonymous? What are the unknown risks if it is anonymous?

MS. BACKLAR: All right. All right.

DR. GREIDER: I am just asking what.

MR. HOLTZMAN: I mean, the risk that is known is that there could be an informational leak.

DR. GREIDER: Right.

MR. HOLTZMAN: And if, in fact, what was later done was something where the informational leak could harm you, then you might be harmed.

MS. BACKLAR: But also the--

(Simultaneous discussion.)

DR. BACKLAR: But also that you don't get information back to you. There is some risk in the fact that you may not find out something that might benefit you to know.

DR. MIIKE: Well, that is in the general thing about what anonymous is. I don't want to get into these other kinds of really low probability risks. It is just

like--sort of like--the initial discussions about informed consent. I don't want to tell them absolutely every possible thing that will happen.

MR. MURRAY: Right. There are parodies of consent forms, you know, that you might be hit by a meteorite on your way to the research site and, you know, can I tell you that there is a zero probability of that? No. But can I assure you that it is very unlikely to happen? Yes.

We can do the .01 Gates principle here. This is that even Bill Gates spending one one-hundredth of 1 percent of his personal fortune probably couldn't find out who you are. That would be a--

(Laughter.)

DR. LO: Well, on the other hand, I think that the low probability--

REPORTER: Dr. Lo, could you use your microphone, please?

DR. LO: On the other hand, I think that very low probability of risk that may have a significant sort of balance for either benefit or harm to the extent we anticipated them, you know, we should try and dispose of them.

I mean, you know, there are procedures we do

in medicine where the risks of dying is very, very, very small, but I think that standard practice would say that there is some risk of, you know, dying from an angiogram.

DR. EMANUEL: Well, let us think through an example. Let us think through an example for a second. All right?

We are getting consent for Physicians Health Study II. All right? And we are going to get the consent. And we are planning to do a series of tests very specific for, you know, some genetic determinants of myocardial infarction. But we are also going to bank a tube of your blood. Okay?

And we don't know what tests are coming down the line when, you know, Carol and her colleagues get done with the human genome. But, you know, we might discover other genes related to heart disease. We might find out that there are other tests we want to do on your blood samples. You know, a tendency to eat high cholesterol food, a tendency to like wine. Whatever. Who knows what it might be.

And we are going to keep your thing and, again, we don't know. We might leak your name but, in general, you know--not in general--all the tests we are going to do are going to be in an anonymous manner on your

sample. You are never going to be identified or linked with it, to the best of our ability.

What is the harm to that individual person that we would identify? We are not going to get back to them with the results. We will publish the results and let the public know.

DR. LO: But see, but at least you have said-- I mean, I think as long as the person consenting--

REPORTER: Dr. Lo, please?

DR. LO: As long as the person consenting understands that the risk that people would be concerned about is the bridge of confidentiality, and we have taken a lot of precautions as are very detailed on pages 2-18, or whatever, and we don't think it is going to happen.

I think that is pertinent to put in the consent form under the risks part. I mean, you put it in context, but I think you don't say we don't know. And you don't say it can't happen. And you don't leave it blank.

So, you know, I think we are agreeing about it. It is just how you present it in a way that puts it out there without scaring people; that it is going to be more likely to happen than it, in fact, is. I think the key is that you have taken a lot of precautions to make it as tight a system as you can.

DR. MURRAY: I want to say one thing. It would be okay I think for us to even sort of publish, as an example, something like the NAPBC consent form. My intuition is we shouldn't draft the specific language of a new form. It will quickly be outdated. There are people who are probably more expert than we to draft the specific language.

I think we ought to say you need to disclose the risks in keeping with the standard, widely accepted principles of risk disclosure in research, but not attempt to provide the precise language.

Now you may and are certainly free to disagree with that.

Bette?

MS. KRAMER: I would think that one of the things that would be the most helpful would be to not to shrink from using sufficient words to have a full narrative that--excuse me--expounds some of the things that we have talked about here around--and other days around--the table.

So that from the language, I think that those who are reading it can get more of a flavor of the kinds of things that we felt were acceptable, the kinds of things that we felt were necessary, even when we don't

make a one, two, three specific recommendation, or sign-off on a particular consent form.

DR. GREIDER: I think that there would be an advantage to having a consent form to which researchers could look for a model from--whether it is our body or some other body--something that is, for instance, available over the Web, because a lot of researchers aren't necessarily expert in thinking about these kinds of things that have been thought about and there can be very good model consent forms which can be easily adapted to a lot of situations.

And I think it might be advantageous for us to at least think about some of those things, or look at other people's forms; to have something available as a model. Otherwise you are throwing everyone out there and saying, "Start from scratch," and that is very difficult.

DR. MURRAY: Well, that is one reason I wanted to put at least the NAPBC form in. And it would be nice to have more than one example of what we have regarded as quite fine versions of it. We have help here at least.

MS. EISMAN: Yes. You had asked me-- You had asked me last meeting to get you some consent forms, and I am still in the process of collecting some of those, but I have tried to get one from each of the categories that I

had defined--clinical care versus longitudinal studies versus clinical research.

And so I have gathered a bunch of consent forms from the NIH for clinical research, as well as at least one longitudinal study so far--the Women's Health Initiative--and also general consent for procedural, diagnostic procedures. And I should be able to get you those copies soon.

DR. EMANUEL: Well, you will definitely will see those before the next meeting, I think.

MS. EISMAN: Yes.

DR. MURRAY: Kathi?

MS. HANNA: I just wanted to add, too, that OPRR routinely does this and, in fact, they are working on templates with a number of institutes on trying to help them get consent forms uniform. More uniform consent forms. So we might--

DR. MURRAY: Would it make sense, Kathi, for us to express our, you know, willingness to help in that development? I mean, as individuals, maybe we should do that.

But to properly see that kind of organization and the NAPBC as the right groups to actually do the drafting. We could then publish, in a Web site, in the

report, several models perhaps.

DR. EMANUEL: And we should look at them before we are willing to sign off.

DR. MURRAY: Oh, absolutely. No, I mean, ones that we thought were good ones obviously. I thought that went without saying.

DR. GREIDER: And then an alternative might be to take ones that we think are good ones and just spend, you know, half an afternoon changing some things so that we are really happy enough to say that we think that this would be a model.

DR. MURRAY: But I guess my idea was this is very kind of texture-rich, and what is a good model for this study isn't-- You have got to tinker with it to get it right for this study. But that is my experience.

DR. LO: If I can make a suggestion. I think that we might view ourselves as sort of looking at the big picture, sort of clarifying the rationale, and leaving it to other groups who are much more involved with the day-to-day business of writing consent forms to work out what the model consent form should look like.

I think we should make a recommendation perhaps that somebody, OPRR or somebody at NIH in the Ethics Division, take this under their wing and really

push it forward, but I don't think that we can make our best contribution actually doing the actual looking at different forms.

DR. MIIKE: This sounds like the draft-looming legislation discussion we had.

DR. MURRAY: Yes, it does. It does. Good reminder. Good reminder. And I think we-- I know the call we made, I happen to think it was the right call that we made, but not everybody may agree with that.

Carol, you look like you want to say something.

DR. GREIDER: There was something that kind of went by in the discussion a few minutes ago that Trish said that I just wanted to get a consensus around the table.

You said that if research is done in an anonymous manner, and the researchers don't get back to the individual with something that might be found with their sample, that that could be a harm to the individual. I had never considered that to be a harm; that the information did not go backwards.

Are there other people that would consider that that is actually a harm to the individual to not have that information? That is-- Am I correct? That is what

you said. That is what I heard you say.

DR. LO: Yes. I would agree, Carol. I would characterize it more under the benefit section. You know, we want you to understand that you will obtain no direct benefit in the sense that, if we find something that may have implication for clinical care--if--we won't contact you because we--

DR. GREIDER: I see it as a non-benefit.

DR. LO: Right. Right.

DR. GREIDER: I don't see it as a harm, but as a non-benefit. So I am just trying to see where other people are on that.

DR. MURRAY: Henrietta reminds me that--and we do have a draft report from the mini-hearings--that there seems to be widely a broad, at least in the public groups with which we spoke, understanding that if you discover something about me in the course of research, that there is some sort of relationship. I can I am interposing. They felt they wanted to know about it. If it could help me, I want to know about it.

DR. EMANUEL: But, but, but, but, but--

DR. MURRAY: Now, that is a perception. We need to understand that was a perception. We may have good reasons for saying, look, the trade-off here would be

between exposing you to potential invasions of privacy versus mostly hypothetical and long-term help.

DR. EMANUEL: I mean, I think this-- Let me say, I think, first of all, this is a framing issue of how you frame the question. I mean, ask anybody if you find something about me in the course of research, shouldn't I know? The answer to that is going to be, of course, yes.

And I think the problem here is this anonymous, you know. We are not actually finding anything out about you. All we are ever going to find out about it is sample number 179, and we can't actually go back unless we are going to say we want to make that encryption not one way, but semi-permeable back the other way.

And I think we need to be clear about that kind of choice. Then, you know, to be used in an anonymous manner, but... And I think that is an important-- I mean, we haven't confronted that issue. I actually would suggest we lay it aside and try to fill in more boxes, because--

DR. MURRAY: I agree. But why don't we give Trish--

MS. BACKLAR: But I just want to say that this is an important choice for this subject. The subject needs to know.

I, as a subject, would want to know what I am weighing against, one against the other. That is all. And it isn't simply a matter of framing the question. You have to frame it in a way that you really give the adequate information to the subject so that they understand, when they make the choice, that they are giving something up, one way or another. That is all. I want it quite clear.

DR. MURRAY: It is not clear they are giving anything up. I would actually put it--

MS. BACKLAR: All right.

DR. MURRAY: I would put it even another way. Given what we know about the common misunderstanding of subjects in research, that it will benefit them, to sort of hold out the prospect of benefit by saying, "Look, if we find out something we will come back and tell you," when we have no expectation of finding anything that will help them, is that it makes a kind of implicit false promise there.

And, in some ways, we may be more deceptive in seducing people into becoming parts of research projects which will not benefit them. It might be a cleaner and more honest solution just to say, "When we anonymous your sample, there is no way to go back and tell you anything

directly. If we find out something really significant, it gets published in the literature, your clinician hears about it, ultimately you learn about it."

DR. EMANUEL: I meant not that people who are consenting. It is a framing question there. That is always true. I am talking about the focus groups and what we heard from the public. I mean, this is a classic case of a framing problem.

And we heard from Jim that, you know, there was a big informational gap. And there is a very big informational gap of people understanding what anonymous research is. So I just want-- I mean, that they want to be re-contacted, I don't think all of the ripples that that implies are fully understood, especially when we get into this, you know, anonymous research.

We should-- I mean, you know, it is worth stating that, you know, today if you, say, participate in the Physicians Health Study and they do a study, they don't go back to you and tell you your sample came out this way. They don't. It is just not the way it is done.

And most-- You know, at least my experience is, when we have found out some sensitive stuff about particular people in a study, the IRB has told us, "No. Don't do that. Don't go back. Don't be tempted to." And

it is. It is everyone's natural temptation.

MS. BACKLAR: But that is the point; to make it very clear.

DR. MURRAY: Even though I am inclined to say don't make such promises and don't do it, I understand the appeal--

MS. BACKLAR: I am not asking--

DR. MURRAY: --and the understanding.

MS. BACKLAR: --to make promises.

DR. MURRAY: Right.

MS. BACKLAR: I want people to understand what it really is about--

DR. MURRAY: Yes. I am agreeing with Trish; that I think this is an issue that we can't just dispose of--not today--and I think we need to have it on the agenda for the next meeting.

MS. BACKLAR: And I think it is interesting that the focus groups clearly--

DR. MURRAY: Yes. That is part--

MS. BACKLAR: --perceive that.

DR. MURRAY: That is part of my--

MS. BACKLAR: And some of your concerns are right in being rooted in that. What we are finding out that people think; that there will be advantages. But

they need to know.

DR. MURRAY: Can we put that aside--if there is one last comment--and move on to the boxes?

DR. LO: I would like to make one last comment. I mean, most of the protocols I have been involved with say there will be no direct benefit to you as an individual. There may be some indirect benefits; that scientists may discover things. But you try to make it very clear that you personally are not going to benefit from this research, if it is this kind of study.

DR. MURRAY: I have recognized someone in the audience. Would you please identify yourself?

MS. GOLDSTEIN: My name is Melissa Goldstein. I am a Greenwall Fellow at Johns Hopkins. I am also a lawyer. I would like to revisit the issue of the model informed consent form.

I think that a model given your stamp of approval--the commission stamp of approval--would be tremendously useful. I think there is a tremendous reliance on model forms in the legal community. And I think that often times it might be a risk management attorney actually approving an informed consent form to be used by a particular hospital and medical school, so I just wanted to throw that in there.

DR. MURRAY: Thank you.

Where are we on the boxes? We have--

DR. EMANUEL: Well, the most important box now is 1c.

MR. HOLTZMAN: Which we can frame, it seems to me, as given that a and e are essentially identical, then we-- Well, no. I am sorry.

DR. EMANUEL: No.

DR. GREIDER: No, no, no.

DR. EMANUEL: Not at all.

DR. GREIDER: b and f.

MR. HOLTZMAN: Yes.

Why would we treat c more favorably in terms of the consent than e? Is there any principle of reason why it is going to be thinner consent for 1c than 1e, or is it a pragmatic argument?

DR. EMANUEL: Well, we had been talking about the idea of presumed consent with an opt out.

MR. HOLTZMAN: Right. Which is, in some sense--

DR. EMANUEL: Thinner.

MR. HOLTZMAN: --thinner.

DR. EMANUEL: Yes.

MR. HOLTZMAN: All right. So if we are going

that route, why are we going that route?

DR. EMANUEL: Well, I mean, some of the reasons we have heard is that the moment of clinical interaction is not a good moment for informed consent. You just don't get informed consent.

And to make it a charade where people think they, you know, feel good because they are getting a sign-off, may not be sufficient; that, in fact, the practicality undermines the aspiration is one idea.

And making it presume puts a different understanding on what maybe the social contract is between people in the clinical context.

I think there is also that idea, which I mentioned when we were discussing 1a, of whether, in fact, people still view these items as their own possession.

Again, that doesn't seem to be the way they are reacting to them in the clinical context, whereas an opt out does give them the option of coming back to us and saying, you know, that isn't. You know, I do view this as somehow attached to me.

DR. MIIKE: I sort of see where you are getting at, Steve, where--

MR. HOLTZMAN: I am sorry.

DR. MIIKE: We may understand the reasons why

Zeke did it that way, but to the outsider it looked different.

And one of the suggestions I made to Zeke, in terms of his opt out informed consent, is that we had talked at the last meeting about, upon discharge, they would be sent out. If they didn't send it back in, it would be--

I had suggested that, since the problem is that the research thing is buried in the overall consent form itself, that we put the research thing after the signature for the general surgical consent and they just have another section right after that where you say, "Oh, by the way, your tissue may be used for research. Do you want to sign this part, too?"

And it seemed to me that would be a simple way of curing it and then you wouldn't have to do the follow up on the outside. And so we are just looking at a way of trying to put more spotlight on it. In that way, then you would still have the general consent rather than an opt out.

MR. HOLTZMAN: Right. And we looked at what the National Action Plan on Breast Cancer has proposed. This is for situation 1c. Right? Is that correct?

DR. GREIDER: Yes.

MR. HOLTZMAN: All right.

DR. GREIDER: It is for 1c.

MR. HOLTZMAN: And so what they are saying is go beyond just the general consent and get a little more specific.

So I am going to take the recommendation here to be that, even in the clinical context, a *de minimus* questionnaire of this nature, at this level, is something which is accessible and reasonable. Do we believe that?

Or do we believe the current argument, if you will, that in the clinical context the people are so unfocused and focused on other things that they won't be able to respond to something like this and, therefore, you either go to an opt out, or you go to something like Larry just said, or you look for the consent later, or whatever.

DR. EMANUEL: Well, I am--

MR. HOLTZMAN: I am just trying to do-- We are running out of time so--

DR. EMANUEL: I think one possibility is imagine we give this during the consent to the surgery or biopsy, or to the blood sample. People are going to feel pressured to sign it, we have heard. People aren't going to give it due consideration because they are worried about recovering from their surgery.

The reason to go to an opt out, rather than an opt in, is the presumption that we will use it unless-- But give them this real opportunity at a better moment in time where they can give it their full attention.

I would, however, caution my fellow commissioners again. When I tried to write this in a generic way, not specific to women getting breast cancer, you know, lines 1, 2--it says 1, 1, 1 in mine--but I think question 1, question 2, question 3, it gets much harder. Okay?

You know, I go in for tonsillectomy. Right? My tissue may be used to learn care to prevent tonsil problems. You know, it just doesn't-- You don't want it that specific, I take it. It becomes a difficult issue.

I would say I am glad to see this revision. I didn't focus in on it thinking it was the same as the one we had seen almost a year ago, but we have removed the genetics/not-genetics issue. I commend you.

DR. MURRAY: Debbie apparently is out on a conference call at the moment.

MS. NORRIS: Do you need her to come back in?

DR. MURRAY: It would be useful I think, Pat, if she could tear herself away.

DR. LO: And when is the-- When is it

proposed--

REPORTER: Microphone, please.

DR. LO: When is it proposed that this consent form be used? Is it with the consent for the vasectomy? Is it--

MS. KRAMER: No. In 1c. You mean--

(Simultaneous discussion.)

DR. GREIDER: When in time.

DR. LO: No. When in time?

DR. GREIDER: When in time.

MS. KRAMER: Oh, when in time. Oh, I am sorry.

DR. MURRAY: All right.

Thank you for joining us. Why don't you ask your question again, Bernie?

DR. LO: One question I had was the consent form that we are given, the proposed final consent form, at what point in a woman's care would you see this consent form being used? At the time of consent to the surgery--

MS. SASLOW: Yes.

DR. LO: --or after the fact?

MS. SASLOW: And during focus group testing, people responded that they would want several days before the actually surgery not, you know, on the table going in.

And that they would want it presented by their doctor preferably, but otherwise by one of the nurses. To have a chance to go home, talk about it with their family, talk to the family about it, and then decide if they wanted to sign it.

DR. LO: So you would give it out at the pre-hospitalization visit and then the patient would have to return it when they came to the hospital.

How would you envision this working--other conditions--where the surgery may be done on almost an emergency basis, where you wouldn't have that several-days window of going home and thinking about it?

MS. SASLOW: I think--

DR. LO: The patient presents with abdominal symptoms, needs an emergency operation, turns out to have colon cancer, and from the time they got sick to the time of surgery they have been in the hospital under stress worried about their condition.

MS. SASLOW: Well, remember that we developed this for breast cancer, so--

DR. LO: No. We are asking you to help us here.

MS. SASLOW: Where they are given the biopsy.

But I think the idea is that, right now, the

surgical consent form has, somewhere in the fine print at the end, whatever tissue we take out is ours to do with whatever we please. And it was to address that.

And there will be collaboration with surgeons, as there has been throughout the process, on how to implement this because it may not be possible even, you know, for a typical biopsy.

The surgeons may not be willing or able to implement a system of doing it before but, at any rate, it should be separate from the surgical consent and perhaps given, in that case, at the same time, or maybe that tissue couldn't be used for research if proper informed consent couldn't be given.

DR. LO: So, if I understand you, you are not quite sure how your group would respond if you tried using this consent form at the office pre-hospitalization visit, but a lot of people just never brought the form back and the pathologist said, "Gee, we don't have enough samples now to do the kind of research we are used to doing."

One option would be-- I mean, one of the options, obviously, are the ones you mentioned. Either trying to give this out as an addendum to whatever forms you sign when you come to the hospital, with all the problems of are you really paying attention to this versus

not using a sample which runs the risk of, you know, having not enough material to do the kinds of wide-ranging studies that folks--that scientists--were talking about.

MS. SASLOW: Right.

DR. LO: Just that the issue--

MS. SASLOW: And it was important that the goal of the whole project was not to maximize the number of people who consented--to make sure that everybody is giving tissue--the goal is to make the patient feel a part of the research process and want to give their tissue, but feel good about giving it and understand why they are giving it.

DR. EMANUEL: This hasn't really been tested? You just had focus groups and then developed the form.

MS. SASLOW: Right. And the Cancer Institute has taken--

DR. EMANUEL: Right.

MS. SASLOW: --some steps to moving ahead with pilot testing, but I don't think they have gotten that far.

MR. HOLTZMAN: I think--

DR. LO: One thing-- I am sorry. Go ahead, Steve.

MR. HOLTZMAN: A quick question. Given that

this is a consent form for anonymized research, so we are dealing in the realm in which presumptively the individual subject cannot be harmed by the results of the research, what was the animus for this?

I mean, you just expressed it as having the research subject as an integral part of the research process. All right.

MS. SASLOW: Uh-huh.

MR. HOLTZMAN: From where did that come as a goal and desire? Was it expressed by the overwhelming majority of people who had been breast cancer patients? I am just trying to get a sense of where--

MS. SASLOW: Right. The whole action plan was started by a petition of consumers, and so-- And Pat Barr, who is the chair of this effort, is a breast cancer survivor as well, and active in the Breast Cancer Coalition.

Consumers want research. They support research. They just want people to give informed consent.

As far as anonymized, remember we are proposing, within a different part of this working group that developed this, a whole system for tissue banking that includes a middle person, like a repository, so that the researcher would not go back to the patient with

results, but would be able to have access to follow up medical information in a unidentified way.

DR. MURRAY: Yes. This, I take it, parallels the kind of system we are talking about. We have used different names for it. But a kind of stewart of the samples.

MS. SASLOW: You can call it a trustee.

DR. MURRAY: Okay. At some point there will be a settling on a particular label for this position, but I think the concept is one that seems to be emerging from several different sources.

Bernie?

DR. LO: Can I ask a question about how you would feel about an opt out provision, where you gave this consent form, but switch the presumption to that, if the tissue would be used for research, unless the person returned the form saying they didn't want it used, would you object to that as not really being consistent with involvement in consent?

MS. SASLOW: I think the group would object.

MR. HOLTZMAN: Why?

MS. SASLOW: I think the whole idea-- Well, then it is not informed consent.

MR. HOLTZMAN: Why not?

MS. SASLOW: You just-- If you don't understand that, you could sign your name to it and not know what you are doing. Right?

DR. EMANUEL: No, no, no, no. That is not-- Say you come in for surgery and either--

MS. SASLOW: Right.

DR. EMANUEL: Well, say you are coming in for surgery. We either send this to you and say, "If we don't get this form back, we are going to presume that you permit us to use your tissue in an anonymous manner."

MS. SASLOW: That is not consent.

DR. EMANUEL: Wait a second. Or, at the end-- Unless you give us the form back. Or afterwards, once you have recovered, sending this form out again.

MS. SASLOW: What if the patient doesn't know how to read?

MR. HOLTZMAN: What if the patient signs this and doesn't know how to read? It is not consent. So the fact that they signed or not signed may not be dispositive. Right?

MS. SASLOW: Okay.

DR. EMANUEL: Well, we have lots of forms that they have to sign. Release of their records to their insurance company for reimbursement. All-- I mean, you

know, the stack is getting larger and larger every day at the hospital.

MS. SASLOW: Right.

DR. EMANUEL: So I don't know-- I mean, there are all sorts of issues with-- You know, we know they don't read those forms, and we know from people that they don't read these forms. So if it is just not that you don't feel comfortable that it is not consent, I guess I am not that persuaded by that.

You know, part of the question is, is whether our traditional notion of consent needs to be operative here or not or whether, in fact, it is suitable for consent. We are telling you what we are going to do unless you take initiative to act otherwise. That is a kind of consent that is presumed.

MS. SASLOW: I think that is sort of like what the status quo is with the surgical consent. You sign this--

DR. EMANUEL: Very.

DR. GREIDER: There is not really an opt out currently.

DR. EMANUEL: You couldn't scratch it out. You could, but people don't. They don't realize it. They never even read that line.

MS. SASLOW: Right.

MS. KRAMER: Or if you read it, you don't know you can scratch it out.

DR. EMANUEL: Right.

MS. SASLOW: I don't want to speak for the entire action plan but, having worked with this group for three years--I don't know--it is just a gut response to you that it doesn't go along--

DR. MIIKE: What would happen if--

MS. SASLOW: --with what they have been doing.

DR. MIIKE: What would happen if, just in terms of operationally by the surgeons, et cetera, that providing the form a few days in advance doesn't work out. Is the group prepared to accept the current status quo?

DR. EMANUEL: I mean, there are reasons. Let me back up.

DR. MIIKE: Let me--

DR. EMANUEL: No, no. I want to elaborate the question.

(Simultaneous discussion.)

MS. SASLOW: It is just when you are dealing with practicalities and they have really developed a process and left it to the community to implement with suggestions. And we have tried to bring in the surgeons

to the process, and the IRBs and all that and, you know, you have to remember that that plan was developed to catalyze a process, and they have brought it to a certain point and they hope it will be used.

And, again, they were willing to accept the consequence of if enough people checked off no, that that is okay. They didn't talk as much about whether people just didn't-- Just ignored it and didn't return it.

DR. MIIKE: No, no, no. What I meant was that, if it turns out unworkable, from the point of view of the surgeons, to have the form be presented early rather than sort of closer to the time of surgery.

MS. SASLOW: I think that is just a preference by the patient. And if it is not practical, it is not going to happen. I mean why--

DR. MIIKE: And they are willing to accept the status quo?

MS. SASLOW: Well, there is nothing they can do about it. Right now, people are signing consent forms at sometimes 3:00 a.m. in the morning as they are being rolled into surgery, and that is not good either, but that is what happens.

DR. MIIKE: I think, Steve, it is a matter of perception.

DR. MURRAY: Bernie?

DR. LO: Can I ask an empirical question? Do you know what the current practice is in obtaining consent for mastectomy?

In my part of the country, I get the impression that the discussion takes place in the surgeon's office days before the patient is hospitalized, but the actual signing of the papers for consent to surgery is done right during the admissions process so--

MS. SASLOW: My understanding--

DR. LO: So would this-- I guess my question is would this require, in some parts of the country, a real change in how the consent process for surgery is obtained?

MS. SASLOW: My understanding is it is doctor-specific; that there are some conscientious doctors who take the time to explain things to their patients and not at the last minute, and there are others who don't have the time or--

DR. LO: Well, it is not just a consciousness issue. I think it is also a paper-trail issue. That if I give the patient the consent form in my office, I have to make sure that the consent entry gets signed and put in the hospital record before I can do the operation.

And so I think, because of those pragmatic concerns, although the discussion, which is the key to this, may take place in the office days ahead of time, the actual opportunity to sign the papers takes place really when you are in the hospital where the papers are right with the operative chart.

MS. SASLOW: Our discussion--

DR. EMANUEL: That is correct.

MS. SASLOW: Our discussion has focused a lot on the fact that this is not just an informed consent form; it is an informed consent process, and so I think what you are describing is the process.

And when I am talking about last-minute signatures, I wasn't taking into account possible discussions before that. That is not what the issue is, or it is what the issue is. That it is a whole process. And it is not-- And the problem is not just when the signing takes place, but did the process take place?

DR. EMANUEL: I guess-- Here is a voice of skepticism. Most of the women with breast cancer who are taken care of, the weeks after they know that they have a malignancy, prior to their surgery and getting it all out, are filled with high anxiety, focusing in on getting it out and having a good cosmetic result.

Adding this to the process, I mean, maybe women who have been through it think that that will, you know, they will be able to focus in on this, in addition to focusing in on either their mastectomy or their lumpectomy. I am just skeptical that that is true, just from all the people I have taken care of.

And, therefore, the idea that this is better consent because, you know, they got the forms in the doctor's office, or something. I mean, I can't see how that is going to be really part of the process; how a discussion about how we are going to use your tissue subsequently is really going to be part of the process.

I mean, most of the women I know about couldn't possibly focus in on that.

MS. SASLOW: All I can say is we focus group tested among breast cancer patients and family members.

DR. EMANUEL: Not prior to surgery though, right?

MS. SASLOW: No.

DR. EMANUEL: No.

MS. SASLOW: And one of the reasons for getting it in advance and having a chance to bring it home to your family is because, you know, your family can help you over the time focus on it.

DR. MURRAY: Steve?

MR. HOLTZMAN: This isn't really directed to Debbie so much as the commission, which is we have here a model of something that goes beyond generalized consent or even opt out--right?--that seeks, in a very simple way, some categories.

To what extent do we feel that this is a model that we would be looking for, for all tissue? In other words, if something like this is appropriate, to what extent is the animus or is the motivation provided from the nature of what is going on in that clinical case when the sample is being collected? All right.

For example, would a--and this is not meant facetiously--a coalition be put together to talk about what we could with a podiatrist's clippings. I don't think so. All right. Well, maybe there would. All right.

So to what extent--

DR. EMANUEL: Is this breast cancer?

MR. HOLTZMAN: Is this breast cancer that we are dealing with?

In the same way in which where people thought about or started talking about genetic tests, what they were really talking about were tests which were

dispositive to the decision whether or not to have kids, or whether or not to have an abortion. And they were highly charged situations. And that is very, very different than a test which has no more emotional or rhetorical content than a cholesterol test. All right.

So I think that is what we need to take a step back and ask, what are we looking at here? Are we looking at a model for all tissue, all uses, or are we looking at a model that may be appropriate in a highly-charged context? And do we want to make those distinctions?

DR. MURRAY: Let me--

MR. HOLTZMAN: Because it may be very valid for that reason.

DR. MURRAY: But what I just heard, Steve, was actually an argument that this sort of model is even more unambiguously valid for other situations in that people aren't in a state of high anxiety when they get their toe nails clipped, or most of these other circumstances and, in fact, can be expected to be able to read these forms in a reasonably deliberative fashion and, therefore, we can attach some moral meaning to their consent signature.

MR. HOLTZMAN: And it certainly could cut the opposite way.

DR. MURRAY: That is actually how it-- I

wasn't trying to be contentious. That is how I straightforwardly read it.

MR. HOLTZMAN: Well, I just all of a sudden-- Just real quickly.

What I know when I think about opt out, and I did think of all the contexts in which it makes a lot of sense to me, why even bother, you know, with getting the informed consent?

If I switched my mind over to the tissue being embryos, I would probably have a very different reaction. I just want to remind us of that.

DR. EMANUEL: I think it is important for everyone to-- I don't want to speak for the commissioners. I think we want to have people informed about what is happening and have an option to exercise their judgement.

DR. MURRAY: Yes.

DR. EMANUEL: I think part of the question is how is that going to be done--

DR. MURRAY: Yes.

DR. EMANUEL: --in an effective way where an effective way is both for them to understand what is happening--the patients--and for researchers to be able to continue to get material, and have access to material in

the future.

And I think maybe part of the skepticism you are hearing from me--I don't know about everyone else--is I am just not sure this process really does that, even on its own terms.

And, you know, in part, I speak as a clinician having cared for lots of breast cancer people. And I think, you know, there is a question of some assessment of it and I think, you know, we are all going to have to make some assessment independent of a full and rigorous set of data.

But I also wouldn't have us throw out presumed consent with a fairly robust opt out option as not really consent. I mean, I think that that strikes me as, you know, we have to think through what it really means, especially if this doesn't work.

DR. MIIKE: Let me tell you-- I am just-- Here is my conclusion. I would opt for a defective general consent system over an opt out system, and I will tell you why. We just dealt with previously collected tissue samples and we are going to be looking for consent before--

Well, I guess that is not true in an anonymous area.

But the second part is that what do you look for in your system? You don't look for a consent. You look for no consent. Because you are going to assume that everybody has consented if there is no form there. And I think that the legal side of me is saying, "Oh, that is kind of a funny situation to be in because you are subject to a lot of errors in that system."

DR. EMANUEL: It encourages researchers to lose paper.

DR. MIIKE: Well, not only that, but--

(Laughter.)

DR. EMANUEL: I hadn't thought about until you said it, but it needs that-- The worse your paper-keeping system is, the better for your researchers, right?

DR. MIIKE: And it is sort of a negative search. It is not a positive search.

DR. EMANUEL: Right. Yes.

DR. MURRAY: A very astute point. Thank you, Larry.

Bernie had a comment.

DR. LO: I want to sort of go back to the issue of this consent form--

REPORTER: Dr. Lo?

(Laughter.)

DR. LO: I just wanted to-- I like to lean back. I am sorry.

DR. MURRAY: In praise of Bernie. Some people just have soft voices. He has a soft, great, I think very comforting voice, but it is soft.

DR. LO: I want to pick up on the point Steve made that the context, the clinical and social context in which we are talking about obtaining this kind of consent for research is terribly important.

And Steve pointed out that there are some clinical situations that are more charged, and sort of embryos is one of the spectrum.

And I would say that there is a social context here which is very important which has to do with what you were saying, with having control and having a voice in what goes on. And this is a disease where traditionally options were not offered and choices were not offered, even after it became clear from the medical literature that there were options and there were choices.

And I think it is within that context that I would say a lot of the skepticism that I think underlay what the development of this; that, you know, there is not a trust in physicians; that they are really not only necessarily doing what is best, but not involving patients

in situations where the weight of the medical evidence is that there are options and there are real choices, and there are very personal choices, and that people ought to be able to choose.

So, you know, it almost sounds as if--sort of to go back to what Jack Killen was saying this morning--that being involved in the process of research as more than just a source of tissue is very important.

And what I was hearing, which I find interesting, is that yours seem to be--

Whereas I inferred that, given a choice between a very flawed consent system that does not really enable participation and choice versus potentially not having enough tissue samples to do the research that scientists want to do, you would opt for the robust consent process and say that is more important that having samples for the scientists to work on.

MS. SASLOW: And take that in the-- That is true.

But take that in the context of this is a subcommittee of a larger working group whose charge was to look at availability of tissue for researchers. So, you know, yes, they will take that as a hit because they wanted to deal with the ethical issue, however their

greater mission was to ensure access and availability of tissue for research.

DR. MURRAY: Let me try to state where I think we may be and give it a little context. Where I think we may be is this.

We have a very creative proposal from Zeke about an opt out system which has lots of advantages. It has two--that I am aware of--main disadvantages, one being the one Larry just pointed out; namely, it sort of rewards sloppiness. And researchers, of course, would never misplace any piece of paper in their office. Yes. Carol will find me the memo any minute now which says that.

The second disadvantage is that, to someone who is suspicious, it can look like a system intended to deprive patients of a voice, however well intended it is. So those, to me, are its two main liabilities.

As an alternative, we have something like the current system, perhaps improved. Well, certainly improved, perhaps vastly improved. We have a sample form from the National Action Plan on Breast Cancer that is in good English. I mean, it is clear. I understand it. There are one or two minor questions about it, but it really-- It is such a vast improvement over the typical consents that I have at least seen.

So we have an improvement over the current system, perhaps a vast improvement. We are talking about changes in the timing of how we give it to people. We give it to them before they come into the hospital. There are lots of ways in which we can do that.

Now this system has some liabilities, too. People may be very apprehensive when they get these forms and may effectively sign it without carefully reading or thinking about it. That is a possibility.

I should point out, however, that we don't have any moral compunctions about acting on the basis of other things they sign at the same time, namely their consent to surgery, in which the immediate benefit/risk ratio to them is--

Well, I mean, the risks are much greater than they are with the little, you know, consent to anonymize tissue research. So, I mean, we do in fact don't regard them as morally infantile at that stage. We do take seriously their signature. Although granted that this--

DR. EMANUEL: They are more focused on that because--

DR. MURRAY: --is more salient. No question. It is salient in a way that this may not be salient. I understand that.

The context is this. There is, I think happily, a reinvigoration of interest in understanding what actually goes on in consent to research. If we have the new--

We have a new program and a whole series of grants that have just been awarded within the past couple of months to study informed consent to research. I don't know if all the members of the commission are aware of this, but this has just happened. It will take a while to see the results filter out.

We have I think a commendable attentiveness not just to the letter of having a signature--I mean, the letter of the law in the sense of having a signature on a piece of paper--but on what it actually means to people to sign that paper. And I think my fellow commissioners have been just terribly sensitive and insistent that we take the meaning, not just the form. I agree with that.

My inclination at this point is to say we should recommend not an opt out system, but an affirmative consent system. That it should be in plain English. It should embody the virtues that your group has helped to introduce into your sample forms. That we-- And that we examine, as an empirical matter, questions like when is the best time to present this? What do people remember?

Do they feel good, and good in the sense of do they feel like they were given an honest chance to give their consent or not?

And simply say, look, the commission does not want to be in the position of making an, you know, ultimate and forever recommendation about specific forms or timing or something. We simply don't have the evidence to do it.

So, on the one hand, recommend something like what you are doing, but also say that, look, as hand in glove with this, we have to have more systematic investigations of whether or not this is meaningful to the people involved.

That is my recommendation. Lots of grimaces and hands. Carol?

DR. GREIDER: So I have been sitting here looking over your shoulder back at the boxes, thinking what we started this conversation on, which was the discussion between Zeke and Steve about why 1c doesn't equal 1e? And I am still trying to figure out why 1c doesn't equal 1e, and from what you have just said, it does.

DR. MIIKE: Yes.

DR. GREIDER: The difference, as Zeke's answer

was, is, in the case of clinical care, which is the 1c, it is more difficult to do the education and to get the information and get it to be truly meaningful.

But just because it is more difficult doesn't mean that you don't do it. You might have the wording be somewhat different on the form given in 1c than 1e because of the very stressful situation under which the form is given, but I don't think that you can have it be a thinner form, if you will, just because it is a more stressful situation.

MR. HOLTZMAN: The difference is that 1e will have the specific protocol at stake with respect to, if you will, the third part of the form, which is the general consent. It would essentially be identical to 1c.

DR. GREIDER: Right.

MR. HOLTZMAN: That is the recommendation.

DR. MURRAY: Now that is just where I am right now. I could be persuaded that I am wrong about that. That is--

DR. EMANUEL: Well, I think when you make your recommendations, you should not say not written in stone, because whatever-- I mean, I think what is likely to happen is whatever we say. If we recommend such a form, if empirical research ever happens--it will take awhile to

happen--and if revisions ever happen, it would probably be, if we know anything about 45 CFR 46, a good two decades or three decades before this gets looked at again.

So I would be-- I think you have to--

DR. MURRAY: I am not quite as skeptical. I mean--

DR. EMANUEL: Okay. Maybe you are not skeptical. But I think we can't have it like, you know, we are going to call for empirical studies, empirical studies are going to happen and then, in the next five years, we are going to take another look at it, because it is not going to be like that.

So I think-- I mean, I do think that, you know, we obviously have come to a nub in where we all, you know, may be persuaded by the practical question of losing, you know, the encouragement to sloppiness, or whatever. I think we need to, you know, think about it.

I would also, you know, recall that we had I think thought about a general informed consent prior to Bartha's visit to us, where she had mentioned this possibility of the opt out being implemented in I think the Netherlands, she said--

MS. KRAMER: (Inaudible.)

DR. EMANUEL: What did you say?

DR. KRAMER: No. I didn't-- But that is a very different society. I think we have to be careful of reasoning.

DR. EMANUEL: Right. Yes. But I think that, you know, that did seem like an exciting possibility at that time, but I think, you know--

MR. HOLTZMAN: I need to voice an opinion. I actually agree with Tom about where we have to come out and, with respect to opt out, or I think even in Sweden where it is not even an issue of opt out; it is just part of the social compact. You get national health care; your sample may be used in anonymized studies.

I think one could sit here--at least I will--and say that is the way it ought to be, and I wish it was that way here, but it ain't. And this is America. This is the land of John Wayne and autonomy. And what I think what we heard from the focus groups is people at least want to be asked. They wanted to be asked. They probably would say yes, and they were quite happy that a benefit came from it for the social good, but they wanted to be asked.

DR. EMANUEL: But I don't think-- I don't think, if we have a full presumed consent, the idea that they are not being asked, or given an option.

MR. HOLTZMAN: Well, I think it is very American. Ask me.

DR. MURRAY: Bernie?

DR. LO: Another point I want to raise is that if we are talking about use of cancer pathology specimens, it seems to me there are multiple points in time that you can get this consent. You could try and get it in the surgeon's office before the procedure. You can get it at the time of the operation. You can get it at the first post-opt visit. You could get it at the first, you know, six-month follow up. I mean, they all have costs in terms of effort, paperwork, delay and things.

But, again, to the extent we are trading off or weighing the ability of patients to participate in decisions versus the sort of convenience of the system and accessing samples, how much effort do we expect scientists to go through to get a thick consent as opposed to, say, we think the research is so inherently important that we want to expedite that or facilitate it as much as possible.

DR. EMANUEL: But, Bernie, I think you are working in the model where all of that happens in the same building, or an adjacent building.

The more likely model is, you know, you go to

your surgeon who has an office, where the surgery happens at a hospital. You then go to your medical oncologist who has an office, which is completely separate from the hospital where you had the surgery. It doesn't use the same kind of form, et cetera, et cetera.

I think you have got a small window of opportunity here. The surgeon's office and the time you get your surgery, and that is it. That is my-- Just from a practical standpoint.

DR. MURRAY: Debbie had wanted to say something before. I don't know if you still wish to.

MS. SASLOW: Yes. When you summarized, you had mentioned the psychological well being of the patient at the time of giving consent and whether that was valid.

Our model provides for the patient to keep a copy of the consent and an explanation of how tissue is used for research and instructions for how to then--

DR. MURRAY: Withdraw.

MS. SASLOW: --change their mind. So if they say yes, they can come back and say no. And it is up to, in our case, the tissue repository to destroy any tissue that is remaining from that person.

DR. GREIDER: Full, informed consent plus an opt out.

DR. MIIKE: But, again, it seems to me this is the exception. We are talking about anybody who goes in for surgery or a biopsy, and what we are talking about is less than 1 percent of that is actually going to be used. So, again, I am looking for the lowest common denominator about what we are going to be asking.

There may be instances, such as this or in some other kinds of studies that Bernie has been involved in, where you might want to go back and get a more informed consent because the likelihood of those tissues being used would be greater than mine, if I am going in for a rotator cuff injury.

So I am looking more at a general consent form; that at least the person knows that, hey, you know, it is not being throw away. It might be used. It is getting stored someplace. But there is no great probability that it is going to be used in this kind of research anyway.

So, again, I don't want to get into an explanation that is way out of proportion to the probability of those tissues being used.

MR. HOLTZMAN: But, Larry, but then the question arises, you are the investigator, you are the hospital who collected the tissue under that kind of

consent. Is that consent sufficient then to use the tissue in research?

DR. MIIKE: Well--

MR. HOLTZMAN: So if what you are saying is they could decide to have more robust conditions--

DR. MIIKE: But I am looking at what we are looking at, which is the tissue universe out there used in an anonymous manner. Yes. And so I am just sort of trying to match our solution with the problem, or the task that is out there.

And, again, I get a little worried when we use these paradigms--situations--where there is a really good possibility that the tissue is going to be used, and it is a serious illness with a lot of serious pluses and minuses that a patient has to consider before they sign.

DR. EMANUEL: We have a four-page packet here on greater than-- I don't know. We have-- We know that there are five million surgical specimens collected in major academic teaching hospitals, and we have no idea of how many community hospitals. That is the number, you know. If we make it a positive, you have got to track for use of 50,000 samples a year, or something.

I mean, we-- You know, we should be serious. Right? If we are making it a positive general consent, I

don't know-- You know, it would be a good idea to know what the end of surgery is. It is much more than five million. I think it is around 20 million in this country. That is the end you are talking about of this form for the possibility of some small number of that being used.

DR. MIIKE: But then also people say that it is a simple matter of just an additional field in your computer database and whether the consent form exists or not.

DR. EMANUEL: Well, you know you are going to require keeping track of the consent form. Right? I mean, that is the whole point of having a signature.

DR. MIIKE: That is why I think that an addendum, just on the same consent form to do general admission surgery, is the way to go rather than having a separate form that you have got to track separately.

DR. EMANUEL: Well, we are not going to get to that level of detail.

NEXT STEPS

THOMAS MURRAY, Ph.D.

DR. MURRAY: Yes. We have a bit under 25 minutes left and we have-- We are at the point of the agenda where we were going to talk about next steps. I hesitate to cut off the discussion about the boxes, but I

think we do need to talk about next steps now.

Can I ask one quick thing? Tell me if I am way off line about this.

My sense is that we just sort of talked about 1a through f; that 2 and 3a-f are all going to include basically the same thing as 1a-f, with the possible addition of some community consultation.

Do I misunderstand it, or is that the likely direction we are headed? So it is going to be that, plus, in each?

DR. GREIDER: Well, we already discussed all the 1 issues, so I think the discussion would be--

DR. MURRAY: Right. So 2 and 3 is that, plus whatever we said about community. So, in way, filling in the remaining dozen blanks shouldn't be a back-breaker.

DR. EMANUEL: Well, we still have to decide whether it is going to be two or three categories. We haven't discussed that.

DR. MURRAY: We have to decide that. And my sense-- What I want to say then is do you think it would be appropriate to put that high on the agenda for our half-day in January?

Remember, we have a half-day as a subcommittee and then a full day as a full commission, then the human

subjects--

DR. MIIKE: I think it will take the whole half-day to discuss it.

DR. MURRAY: It may. It may. Except I have a feeling we-- We have a lot of clean up of stuff to do from today even, but I have a feeling that we are fairly close on the community consultation issue.

Would that be appropriate? Okay. Let us make that an agenda item.

In that case I have several other things I would like you to--the staff and I--would like you to please help us with.

The first thing is, in your packets, you should have received a draft outline of the report. It says "Draft -- December 7." We have Kathi Hanna to thank for this. I suppose I will ask you to do two things.

One is to take a quick look at it, if you haven't already. If you know immediately of anything that needs to be changed-- I think changing the order is the least important thing. It has more to do with are we covering the right issues? Is there anything of significance being left out? Is this complete?

Now, if you don't see anything today, you should please take this with you, make it the first thing

you study when you get home, or on the way home, and get in touch with Kathi, the NBAC staff, and actually the rest of the subcommittee, myself included.

DR. GREIDER: Can we ask questions now?

DR. MURRAY: Yes, absolutely.

DR. GREIDER: The two first points, "medical" versus "genetic" information. What does that mean?

MS. HANNA: Well, I was hoping you would all let me know today what that means. I think I need some input on that. I keep hearing that, by and large, it is not different, but I think there is two reasons why you are going to have to be very explicit about why you are saying that.

One is just from the point from which you are arguing your recommendations; you have to be clear about that.

But also because this is the Genetic Subcommittee and I think you need to make it clear to the readers of the report why, right up front, you chose to really not make a very clear distinction.

So I would like perhaps a few volunteers that I can pick your brains a little bit, either through e-mail or over the phone, and help me develop the explanation of that whole argument.

DR. MURRAY: It is actually I think a good idea to have us each take some responsibility for pieces of the report. You can take responsibility for more than one piece. I would like to have everybody involved in at least one piece.

What does it mean to take responsibility? It means to be a primary reader of drafts, whoever generates the draft. In some cases, depending on your wants and abilities, it may mean helping to draft bits of it. I mean, a paragraph here, et cetera. But I would like to see some specific assigned responsibility, self-assigned, so I am going to volunteer to help with that one. Anybody else?

MR. HOLTZMAN: I will help on that one.

DR. MURRAY: Steve is going to help with that.

DR. EMANUEL: Our understanding there is that we anticipate that our recommendations are going to apply beyond genetic tests; that it really-- It is really any research on stored tissues.

DR. MURRAY: Right.

DR. EMANUEL: And as to whether that applies beyond that to stored information, medical information, I think is also important because the appropriate section in the regs is broad.

Let me just quickly remind people it says, "Existing data, documents, records, pathological specimens or diagnostic specimens." Okay. That is what the current and existing regs apply to.

DR. MURRAY: Right.

MS. HANNA: I think this has to be considered in the light of the fact that there are a lot of definitions of genetic information that are being floated around right now, both in the pending legislation and in existing legislation. And so, to the extent that the subcommittee can either concur or refute those, I think it would be useful.

DR. GREIDER: So we need to cite some of the things that are already out there and say, "It has been said that there is a distinction and we think that there is not because..."

DR. EMANUEL: Or it is not relevant in this category.

DR. MURRAY: I think that is right.

DR. GREIDER: Yes. We just have to be explicit.

DR. MURRAY: That is right.

Who would like to help with III, Public Knowledge and Beliefs? Remember, we are not going to ask

you to do things you are uncomfortable with. At a minimum though, it would be someone that Kathi could talk to and share drafts with for comment.

DR. MIIKE: Okay. I will volunteer.

DR. MURRAY: Larry, thank you.

If you don't volunteer I may twist your arm in private later. I don't know if that is informed consent. It is a warning though.

Human Tissue Samples in Research? Carol. We may, since David is not here, we are going to assign him to that section.

DR. MIIKE: You know, on that one, there seems to be--the last dash of the second bullet--everything else seems to be very scientific, but then the uses that such information might be put seems out of-- It doesn't match the rest of that. It gets into the social implications type area. So maybe-- So I was thinking maybe that should not be part of that section but--

DR. MURRAY: Part of the Overview?

DR. MIIKE: Yes. Part of the Overview.

DR. MURRAY: Okay. I tentatively put it up there.

DR. MIIKE: And obviously diagnosis and treatment stays in there, but the public health planning,

managed care decisions kinds of things should really go up there.

DR. EMANUEL: I would also recommend it is not clear to me that existing scientific medical policies/directives/guidance, i.e., the current debate, appropriately goes under that.

I mean, what I took this section to be is what are the samples we have and how are they used? What are the sort of kind of paradigmatic cases? Whereas the recommendations floating out there might be more appropriate to either Status of Current Policies, VI.

DR. MURRAY: Okay, V, Principal Issues to Consider.

DR. GREIDER: The volunteer's name is right in the front there.

DR. EMANUEL: Thank you, Carol.

MS. HANNA: I have kind of an operational question on this section because obviously Section V and Section VII are linked. V is really the discussion I think of the issues and then presumably, if today is any evidence, then VII is kind of your walk through the boxes.

So, Zeke, maybe we can talk at some point about how to separate out the kind of discussion versus the recommendations.

DR. EMANUEL: Or one question is whether-- I mean, the way you have structured it here, I think either V goes after VI--that was going to be my next recommendation--or V goes after II. That was, you know, you have got to have the framework either right up at front, or right before your recommendations.

Now, I think there is a reason-- There might be a good argument to have V after VI because we are, in some sense, re-writing the kind of presumptions. You know, we are no longer interested in anonymous tissue. We are combining research and clinical in many categories.

DR. MURRAY: I think that is right. I think that is a tentative reorganization, so we are basically switching V and VI.

DR. EMANUEL: So then what we have is, I would estimate, a very brief paragraph, a brief chapter--sorry--outlining the sort of framework we are adopting and the justification for that framework, and then a much more detailed, "This is what we mean in each one of those boxes," which would be VII.

DR. MURRAY: Yes. One thing I don't think I see here is the sort of fully fleshed out discussion of the ethical, ethics and values issues.

MS. HANNA: Right. And, I mean, they are kind

of lumped under Section II right now.

DR. MURRAY: Right.

MS. HANNA: And we, Tom, we had talked about this a little bit; that I felt like we were still missing that piece that would talk more generally, not from a religious perspective, but from a more ethical perspective on things having to do with harm to individuals, privacy, wrongs.

DR. MURRAY: Yes. Yes.

MS. HANNA: Group harm.

DR. MURRAY: What is the sense here of the commission? Should we-- Has that become a separate chapter? Does it become a separate chapter?

DR. EMANUEL: Yes. It should be IIA there.

MS. KRAMER: IIA?

DR. MURRAY: Okay.

DR. EMANUEL: That is where I would put it.

DR. MURRAY: Yes.

DR. MIIKE: Then should religious perspectives go in there rather than Public Knowledge?

DR. : I think so.

DR. MIIKE: I am just trying to see--

MS. BACKLAR: And I would wonder if you would like Public Knowledge and Beliefs before that. It seems

odd to do the ethics first--

REPORTER: Could you use your microphone, please?

MS. BACKLAR: --and then Public Knowledge and Beliefs.

REPORTER: Use your microphone, please.

MS. BACKLAR: Oh, I am sorry. It seems odd to do ethics before Public Knowledge and Beliefs.

DR. MURRAY: I actually agree with that.

DR. EMANUEL: Really?

DR. MURRAY: Yes.

DR. MIIKE: Well, except that the ethics part is included in the current debate. The public perception is not. I mean, what has brought this issue to the fore and what are the kinds of things that are being discussed?

MS. BACKLAR: That is true.

DR. EMANUEL: My own view is that I would have moved the public perception after the Status of Current Policies because, in some sense, the public perception, you know--

Here is my line. We have an introduction to the problem, an overview of the current debate, the ethical and religious values at stake, the kind of samples we have, and research that we are likely to use them for,

the kind of rules and regs we have, and where the public weighs in, or might not weigh in. And then we talk about our framework.

DR. MURRAY: I am easy, Zeke. That sounds fine.

DR. MIIKE: So that goes after the current VI.

DR. EMANUEL: Yes.

DR. MIIKE: And then your V goes after the current III.

DR. EMANUEL: Right. Is that clear, Kathi?

MS. HANNA: Yes.

Now, the one thing that doesn't really-- I mean, if you look under Section VII, what I have kind of loosely called "security mechanisms," which is the more procedural handling of the tissues and the encrypting and all of that, at the last meeting we talked about it a little bit more extensively that, you know, the wall, the fire wall. We didn't really talk about it today.

But at some point I think that has to be more. People have to agree really on what is being said there. So maybe at the next meeting.

MR. HOLTZMAN: Could we get a hold of Klausner at the NCI because I was talking to Eric Lander last night and he Botstein(?) put together something they sent to

Klausner on the one-way permeable membrane about a year and a half ago.

DR. MURRAY: There is also a piece in the latest edition of *The Journal of Law, Medicine and Ethics* about medical records privacy, including various kinds of ways of protecting, and some of the dangers. So I will be happy to share those with you. Well, actually copies of the *Journal* are going to all the members of the commission.

MS. HANNA: Right.

DR. MURRAY: So you will be getting it.

DR. EMANUEL: Kathi? Maybe we could go down VII for a second. I think this retrospective versus prospective, which we have renamed, really belongs in V, what will be future VI, or whatever. Sorry.

DR. MURRAY: Let us use their names.

DR. EMANUEL: Okay. The general framework that we are using.

DR. MURRAY: Yes.

DR. EMANUEL: Then I think we need to talk in general here about the kinds of protections we are interested in. The anonymity protections and, therefore, the one-way permeable membrane, the issue of trust, the kinds of levels of consent.

And then I think we go, in this chapter, to the different boxes. You know, what is the judgement in each of those boxes?

And actually, as we are talking, as we were--

DR. MURRAY: Except the boxes collapse. Some of them collapse.

DR. EMANUEL: Right.

DR. MURRAY: Say all research on identifiable tissues looks like--

DR. EMANUEL: Right. I would only raise a flag in people's mind. In what way now, on the samples to be collected in the future, is clinical research-- Is clinical-- How is the sample collected under the guise of clinical care, different from samples collected under the guise of research?

Have we now collapsed, as we did previously, those two columns, if we are no longer making the presumed consent versus general consent? If we are making it all general consent, I submit to you we may, in fact, have collapsed the research and clinical care section.

MR. HOLTZMAN: We have with respect to general consent to unspecified studies.

DR. EMANUEL: Yes. I think people ought to think about that for the opening of the next meeting.

DR. MURRAY: I didn't get--

DR. EMANUEL: Sorry to--

DR. MURRAY: I didn't get to-- That is okay. I didn't get to finish assigning sort of accountability for these sections.

Steven and I are going to look at the Overview.

We now have a chapter on Ethics. I am certainly going to stick my nose in that one. Who else would like to work on that one in particular?

(No response.)

DR. MURRAY: Public Knowledge and Beliefs. Larry.

Human Tissue Samples in Research. Carol and perhaps David.

Principal Issues to Consider. We have nominated Zeke.

DR. EMANUEL: Right.

DR. MURRAY: Anyone else?

(No response.)

DR. MURRAY: Status of Current Policies. Who would like to help with that?

DR. EMANUEL: I certainly could.

DR. MURRAY: Yes. Well, some of us haven't--

MS. BACKLAR: I haven't volunteered for anything.

DR. MURRAY: Policy Options and Recommendations.

DR. LO: I was going to volunteer for that.

DR. MURRAY: Bernie is volunteering for the Policy Options chapter.

Zeke is volunteering for the Status of Current Policies.

There are a few of us who have been relatively quiet.

MS. KRAMER: Noticeably. Where would you like me to go?

DR. MURRAY: Bette, since you were so involved in the Public Knowledge and Belief piece and helping to put the idea of the mini-hearings together, would you be willing to work on that one?

MS. KRAMER: Uh-huh.

DR. MURRAY: Thank you.

Now, we don't have anybody-- Well, no, that is a sub-issue.

And, Trish, did you have anything in particular you wanted to work on?

MS. BACKLAR: No. I mean, I was interested in

the section for the discussion groups and also the ethics. We already have been discussing these.

DR. MURRAY: Okay. So I am going to put Trish down for the Ethics chapter and for the old III.

MS. BACKLAR: But I am concerned--

(Technical difficulties.)

DR. MURRAY: Okay. Any-- I need this. Any further thoughts on that, let us share it with each other.

Do we have any pieces that we need to get written that we need to hire somebody for? We will--

We thought that there might be a good role for, say, a 2,500 word piece to summarize the ethical issues on both sides, which we thought one of the contractor's paper would do, and it did some other very useful things, but not exactly that, and so if you have any thoughts about who might do that, we do have some thoughts about trying to get that done rapidly.

MS. KRAMER: Tom?

DR. MURRAY: Yes, Bette?

MS. KRAMER: Would it be possible for us to get a new chart of the boxes with a synopsis of what we have done?

DR. EMANUEL: What we have agreed to?

MS. KRAMER: Uh-huh.

DR. MURRAY: Yes.

DR. EMANUEL: You mean just 1a-f?

MS. KRAMER: Uh-huh.

DR. EMANUEL: Yes.

DR. MURRAY: Zeke, the offer is that, if you even just want to mark it up by hand, the staff will produce it, or if you want to do it--

DR. EMANUEL: All right. I have it on diskette and I will e-mail a thing to you, Henrietta.

DR. MURRAY: Thank you. I should note that we want to think about the meeting in January; about the issues that we just want to deal with. We know we are going to talk about the community consultation piece on the first half-day. But the things that we really would like to see brought up for the full commission, possibilities.

And there are things that the full commission, the other half of our commission, has been working on, including issues about informed consent, you know, the composition, behavior, et cetera, of IRBs, the idea of the community consultation research, et cetera.

So I don't think we need to make a decision at this moment, but please think about which issues you would like to see us most especially focus on in our joint

meeting.

DR. EMANUEL: Tom, I think, you know, we have had a number of meetings without them. If we don't, in some sense-- I mean, one of the big things that we have to go through to get them up to speed and understand, we need some brief overview of the current debate.

DR. MURRAY: Yes.

DR. EMANUEL: We need some summary of the available human samples. I think we need to remind them about the current policies. They haven't focused in on it. And then talk about our framework and where we come out.

I mean, it seems to me that, until they get all those pieces in place, they can't even, in an educated way, participate in the discussion and, you know, that is frustrating for them and it is frustrating for us.

DR. MURRAY: Well, our hope and expectation is that they will have at least a draft of major sections, drafts of major sections of the report by then. That is our hope.

DR. : By January 9th?

DR. MURRAY: Before January 9th.

DR. EMANUEL: But I think--

DR. MURRAY: The meeting is January 9th?

MS. HYATT-KNORR: It is the 7th. It is the 6th and 7th.

DR. EMANUEL: Yes. It is the 7th.

But I think much more realistically we should plan for maybe either a half-hour or hour dog and pony show, frankly.

DR. MURRAY: No. I think that is right.

By the way, I have put in a bid, because I think our report is closer to fruition than what is going on in the Human Subjects Committee, for us to have more time to present our report than if we just split the meeting 50/50, which means we would have to then say, at another future full meeting, that we give them more than half the time.

But I think that is utterly appropriate and it is in the commission's interest and in the researcher's and subject's interest to get this thing done as quickly as possible. So I will put that-- I will continue to press that bid.

I think Zeke is right. We will have to take a half an hour, or an hour to just sort of lay it out for them, and then we should have just the issues that we think are crucial to discuss before them.

It has been pointed out to me that it would be

useful to involve-- There have been voices that have been present pretty continually, continuously in our deliberations, and there are other voices that haven't been so present, other perspectives.

It would be helpful for us to identify other groups, individuals, who we ought to be showing the report to, talking to--whatever--so that we make sure we are not, you know, that we haven't ignored significant perspectives.

So if you would think about that, that is another thing which you could communicate by e-mail to the rest of us and to staff. That would be very helpful.

Bernie?

DR. LO: A question about potential other bits of information you want to gather; to go back to what we were talking about right before we talked about next steps.

Do we want to try and compile some compendium or article on what is being done to improve informed consent to these types of studies, and where we stand, and what the likely time-table is? I mean, what some of the sample documents are?

DR. EMANUEL: An appendix, you mean?

DR. LO: Well, just so we could gather all

that so we know, you know, against what moving target are we taking our--

DR. MURRAY: Yes. What is the best way to accomplish that, Bernie? I think it is a good idea.

DR. LO: I don't know if staff can do it. If there is someone we could contract to do it who is--

MS. HYATT-KNORR: I think we ought to give it some thought and get back to it. Let us say tomorrow.

DR. LO: I know. But people in--

MS. HYATT-KNORR: I think it is a two-pronged effort. I think you want to do a literature search and you want to write something up. So let us give that some thought and get back to you tomorrow.

DR. MURRAY: And it may be that the other half of the commission has already done some of this, so I will count on staff to brief us on that and communicate with us all soon.

Any other urgent items? We are approaching 3:30 p.m.

Bette?

MS. KRAMER: Is this on?

Is there any information out there that we could have at our disposal to help us as we are thinking about community issues?

DR. LO: We are going to try to ask Jack Killen.

DR. MURRAY: We are asking-- Yes. As Bernie said, Bernie and I approached Jack Killen. We thought what he had to say was very interesting and we encouraged him to write it up, and he had the same idea. I hope we will have something from him.

I don't-- I am not aware of a sort of really good evaluation of scholarly resource on this. In fact, I think we have identified a lacunae in the literature, which ought to be filled as rapidly as possible, but probably it won't be filled rapidly enough to be part of our deliberations. It will take a while.

DR. EMANUEL: I forget whether we have seen Charles Beers'(?)--

DR. MURRAY: No. I have not.

DR. EMANUEL: We haven't shared it yet. I have seen a prior draft.

DR. MURRAY: I have not seen it. Could you share-- Can we see that?

MS. KRAMER: That is the paper you said that was coming.

DR. MIIKE: You know, maybe over two years ago, Gary Ellis and OPRR was very interested in the issue

about communities and community's responses and information in terms of our research projects.

Remember, when we first started as a commission, there was the Canadian report that talked about collectivities and things like that?

DR. EMANUEL: That report is reviewed by Charles and sort of-- And that actually turns out to be a derivative report of something that went on in Australia, but it has got some, you know-- I mean, part of the virtues of his paper is he outlines the pluses and minuses, but doesn't lay out sort of prospective positive this is where we ought to go.

DR. MURRAY: In case this is mysterious, as I understand it, this is a paper commissioned by the other half of the commission, the Human Subjects group, so that paper, as soon as it is in a suitable form, which may be already for all I know, ought to be circulated to all of us.

ADJOURNMENT

THOMAS MURRAY, Ph.D.

DR. MURRAY: If my hat were here instead of over there, I would take it off to the commissioners. I think you have done tremendous work today. Thank you all. Thank you for the guests who have helped us in our

deliberations. And thanks to staff of NBAC who did a great job of getting us ready for this meeting and supporting us.

Have a good holiday. We will see you all in January. Good bye.

(Whereupon, at 3:32 p.m., the meeting adjourned.)