NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

WELCOME

DR. SHAPIRO: I would like to call our meeting to order. We have a long and a full agenda today so I think we better get under way.

For those of you that were not with us yesterday, I want to announce once again that we have to my right, Eric Meslin, who is now our director. I want to welcome him. We are very fortunate to have been able to attract him. As many of you know, he has had a series of interesting and distinguished posts. We have, as someone mentioned yesterday, just pirated him from ELSI and we are very pleased to do so. I welcome him.

I will take the opportunity, also, once again to thank Bill Raub, who has served in an acting capacity for us for a good part of last year.

Now, we will begin this morning by discussing the ongoing work of the Human Genetics Subcommittee which met yesterday and had what I thought was a very interesting discussion and we will hear more about that in just a few moments. I will turn to Tom. That will be our first major item on our agenda.

Most of the afternoon we will be doing work with the Human Subjects Subcommittee.

And we have a few very important guests here today as well.

There has been a change in the agenda, just a rearrangement of items. I think everyone has got a copy of the current agenda in front of them. If you would just take the issue "Future Commission Research Activities" and put that as the first item after lunch that had been, if I remember correctly, the last item of the day. I have put that first after lunch because unfortunately late in the afternoon I will have to leave perhaps before we are able to adjourn and I wanted to make sure as many of us as possible were here for that discussion.

If I do have to leave while some of the discussion is going on I apologize to my fellow commission members and to any guests who may be participating in the discussion.

So, we have quite a few items and I think we just ought to get going and let me turn first, then, to Tom and the report of the Genetics Subcommittee.

Tom?

If I could just make one more comment. Someone said yesterday the sound system here is the rock star variety, that is you have to talk very close to the microphone in order for it to really work and please jump

up and wave your hand if we are not -- to our technician and helper here if we are not doing this properly.

So thank you very much.

Tom?

REPORT FROM THE GENETICS SUBCOMMITTEE:

TISSUE SAMPLES REPORT

DR. MURRAY: Thank you very much. It is, indeed, a shock when one finds one's chairman in the morning on CNN discussing the previous work of the commission and discussing it very articulately.

It is not true that the commission is going to fund its work from here on in by establishing "Clones-R-Us," is it, Harold?

DR. SHAPIRO: That is not true. As you know, as everyone knows, I am sure, that cloning is again in the news. It is interesting how this sort of gets itself into the news again and you have seen it in this morning's paper. As far as I can tell, nothing has changed since we discussed this last time so we will not take that issue up again at this moment but thank you for noting that, Tom.

DR. MURRAY: The Genetics Subcommittee is trying to finish up its work on the issue of the use of human tissue samples. Our interest in the work was, as many of you know, was motivated by a variety of factors.

One is we know that there were a lot of tissue samples out there. We had no idea quite how many. We have a much clearer idea. We have a very conservative estimate but a much clearer idea now of how many. It is well over a quarter of a billion and it may, in fact, be as many as half a billion tissues, identifiable tissue samples, in various tissue banks and collections in the United States.

A second motivating factor was that these samples, which have been collected for as long as a century and were thought to be of some scientific interest, now we understand if they are properly stored can have analyzable DNA, which can offer an increasingly vast amount of information about the individual from whom the DNA was taken.

Thirdly, a series of commentaries, some by official groups, some by ad hoc groups, some by individuals suggesting what ought to be done about research on such tissue samples, both samples collected previously and samples to be collected in the future, came to some very strong conclusions and in many cases contradictory conclusions. So those factors together led us to take on the tissue sample issue.

What we are going to do this morning: We will hear from a couple of guests. As you see at 9:30 and 9:30

Susan Old from the National Heart, Lung and Blood Institute and then Patricia Barr with the National Action Plan on Breast Cancer but we will have till about 9:30 to begin our conversation.

We will add those two folks to the conversation. We will resume it again and we will be able to continue on till around 11:30, at which point there will be comments by Harold and statements from the public. So we have around two, two-and-a-half hours of actual deliberation, and we look forward to having the members of the other subcommittee join us in these conversations.

Our goal for this morning is to talk about four, perhaps five, things. Some of them will take more time than others.

I am going to do the first thing and I hope it will not take long at all.

I am going to describe and try to defend our decision to talk about research conducted in an anonymous -- research conducted on tissue to be used in an anonymous manner and explain how that differs from some of the ways people had conceived of these tissue samples prior to our work.

Secondly, Zeke Emanuel will describe the matrix that we have been using to look at possible cases. That, I

think, will take the longest time.

Bernie is going to talk about the concept of community consultation. People have described it other ways, community involvement, et cetera. We have been using the phrase "Community Consultation" as an ingredient for some of the situations that we intend to encounter and we expect to encounter.

Fourth, Trish and Larry, and I think they have enlisted some other folks to help them, are going to take on the issue and we actually want your help, the other commissioners' help as well, in discussing the issue of whether to have this wall through which information is sent with the identifying information stripped off. Whether to have this wall be perfectly inpenetratable, or as perfect as human wile can make it, or whether, in fact, to allow under certain, perhaps rare circumstances, people to go back and to try to rediscover the identity of people used. This was a contentious issue and we will talk about that. Trish and Larry will lead that off.

The fifth thing, and I think if we do not get to that, probably I think it is a little bit less controversial but I suppose I would lead the discussion of that, is some mechanics of the consent process that we have in mind. That is our agenda. It is a very ambitious one

for two to two-and-a-half hours but we will do our best.

Zeke, did you want to put that up?

DR. EMANUEL: Yes.

DR. MURRAY: Yes. Why don't we put that up. Thank you.

While Zeke is -- right.

(Slide.)

This will be helpful all through our conversations this morning.

By research conducted in an anonymous manner what we mean is this: One problem we had was many of these tissue collections for a variety of reasons would be inappropriate to strip identifiers from the tissue held say by the pathology lab at the teaching medical institution so, therefore, did we have to think about those tissue collections as identifiable. Well, clearly in the form in which they are held by the pathology laboratory they are identifiable and need to be identifiable.

What will that mean in terms of any research that might be done with some tissue collections? Well, it struck us after a considerable amount of conversation that the most important -- that it made more sense to think about anonymity in the context of the particular use of the tissue.

If, for example, I have -- in an extreme case I have a series of fully identifiable tissue samples and I send them on to another scientist with every piece of identifying information stripped, there is nothing except the raw tissue, and that is what the scientist works with. It seemed odd to think about that as "identifiable" tissue. That scientist would have absolutely no way of going back and finding out from whom that tissue came so we came to a model of thinking of the tissue as used.

It struck us that we accomplished the goals of protecting individual privacy and protecting individuals against potential discriminatory uses of genetic information about them if we, in fact, endorse a process by which a scientist could make a request for tissue, have the tissue sent with perhaps some information but not enough -- not sufficient information to identify the individual from whom the tissue came and to say that in that sense the tissue was being used in an anonymous manner.

There is, what Zeke has labeled, an encryption barrier that is better than the metaphor of a fire wall. It is an encryption barrier which involves the stripping of a considerable amount of information. It might contain such things still as a medical history or at least the relevant points for the disease in question. It might

contain information about sex, about background, about geography and some other matters but not sufficient information to walk back, as we use the metaphor, walking back across the barrier and figuring out from whom the tissue came.

So if you see the phrase or a variance of the phrase "research conducted in an anonymous matter" that is what we mean by it. It is the tissue samples and whatever information is bundled with the samples has gone through this encryption barrier and it would be impossible or unreasonably -- reasonably -- I am not sure quite what the phrase is there but it would be reasonable to think that the researcher could not walk back and get the individual's identity from the information the researcher has even with the aid of other kinds of publicly available databases.

That is really all I need to say.

I would like to ask the other members of the Genetics Subcommittee to elaborate or correct what I have said and I would like to invite the other members of the commission to join in.

David?

DR. COX: So I think you have very fairly

stated the attractive aspects of this approach to dealing with stored tissue samples but it is particularly relevant for the large numbers of pathology samples that presently exist and then the clinical samples that are going to come in. It does not very well take into account potential future types of research that are going to require closer and closer interaction between the researcher and the subjects.

Although it does take into account subject's viewpoints from the point of view of their privacy it does not take into account the subject's involvement in the design of the research studies at all.

The other aspect of it is that in many ways for researchers it perpetuates a distancing of researchers from the research subjects at a time when the whole direction of much of the science is an increased involvement in relationship between researchers and their subjects so that I, for one, have sort of a difficult time balancing these different issues and

I just wanted to mention what some of the down sides of this approach are.

The final point that I would like to make is that any kind of such barrier that is put up to protect people is only as valuable and only as effective as its

ability to limit loopholes for people to go through it. I must say that it is easy for commissions like this to talk about how encryption completely limits loopholes and on the other hand in reality have it simply be on a piece of paper and not how it works. If the commission sets up things that work on paper but does not work in reality I am not sure that we are helping.

So this is not -- I just wanted to talk about what some of the negative sides of this approach are and perhaps by considering them and having some flexibility with this we may make it more practical for research in the future.

DR. MURRAY: I certainly agree with the latter two points you made as I understand them. I mean, if we recommend something which either is impossible to implement in practice or would be widely abused then I think we have not done our job well. I do not think that will be the case but we need to be cautious about those options.

In the former you are concerned about the distancing of researchers and subjects, et cetera, but this is not the only model as you know for research with tissue. There is -- you can do research with tissue where the tissue is used in an identifiable manner but a requirement is then upon the researcher to get express informed consent

for each -- for the particular use of the tissue envisioned is very powerful.

So I think there is not a distancing -- we are looking at the -- we are looking at cases in which the researcher for a variety of reasons may not need that kind of close contact and may want to use either large amounts of tissue or tissue that is with relatively small amounts of additional information. So there are other ways of doing it. There need be no necessary link between this proposal and a further distancing between researchers and subjects in those kinds of cases where distancing would be inappropriate.

DR. COX: Just one quick follow-up point. I quite agree with that except I am basing my comments particularly with my experience as a geneticist because genetics research -- in fact, we are the Genetics Subcommittee -- I am not saying that genetics, you know, is inherently different from other types of medical information but genetics is only as good as the definition of the phenotype hooked up with the genotype.

So, I think, at one sort of fairly extreme end of researchers that need to have close relationship with the phenotype I think the geneticists are very much on that one end. So that is sort of why I am making my comments.

DR. MURRAY: Right. Thanks, David.

Alex?

MR. CAPRON: I think that I would really understand this only as I begin to see what consequences you think grow from the description that has been given here but I would like to begin that process by asking you whether the category here is the one which is described on the charts that we were given as samples that are to be used in an individually anonymous manner. Is that correct?

DR. MURRAY: I have not seen this morning's version of the chart. That is my understand, yes.

MR. CAPRON: If that is the case I want to suggest very strongly that we consider separating into two categories what you seemed to have lumped into one. As I understand it, there are any number of --

DR. EMANUEL: Alex, maybe I could explain the chart before we already divide it and we break it apart.

MR. CAPRON: Well, let me make my comment first because I think if -- you can respond to it.

As I understand it, there are any number of situations in which researchers are interested in samples which have no identifiers at all on them, that is to say if they are looking back at the PKU samples and they have

10,000 of them and they just want to ask is another -- what is the prevalence of another gene in the population of babies born in Denver in 1996 or something. They do not have to know anything about it and that is truly an anonymous sample.

It seems to me what you have described here is something that would be more correctly described as the use in an encrypted manner and to lump together something which is anonymous with something which is encrypted is to me a basic mistake and I would be very disappointed to see us move in that direction.

I look here and I see -- this is a problem with graphics rather than having text -- what I see here is something which says it has a sample and on one side it has the name on the sample and in another one it has a number, and then it has something called "medical record," which on one side has a name on it and another has a number on it.

Now you have made certain comments, Tom, and I think this is relevant to David's comments a moment ago, about what that information would be. But if we were to literally publish this chart as our explanation of what it meant to encrypt something I would say that simply underlines to me the problem with calling this anonymous research.

I mean, if we have a medical record from which my name has been removed and been replaced by a number we have a lot of information and I cannot believe that someone looking at that -- a clerk working on the project who knows that I was in for a removal of a cancerous growth and you are now looking to see some other genetic factor would not be able to look at that and say, "Oh, that is Professor Capron."

DR. MURRAY: That would not be anonymous, Alex. You misunderstand what we are saying.

Zeke will have some comments.

DR. EMANUEL: I think --

MR. CAPRON: And then, Zeke, as you do this could you explain what the results "Name-A," results "Name-number-A." What that X means and what those are?

DR. EMANUEL: Alex, this is why I suggested before criticizing the boxes I thought we would explain why we got there. Maybe I can explain why we got to where we have and how this graphic fits in with the thinking because, in fact, we began exactly where you and most of the recommended statements begin exactly where you are, which is making more than a few distinctions.

So everyone has -- all the commissioners have

this but I am going to use some overheads so we are all on the same page as it were.

(Slide.)

And I want to, in part, talk a little bit about the evolution of the thinking because this is not where we are today. All right? But I think by trying to explain a little bit of the evolution of the subcommittee's thinking it will become clear why we have gotten rid of some of the distinctions. So this is sort of transitory intermediate framework that we use and then we will talk about it.

Is that in focus?

COMMISSIONERS: No.

DR. EMANUEL: This will not do this.

I apologize.

DR. SHAPIRO: Help is coming.

DR. EMANUEL: All right. You have it on a sheet of paper. Okay.

If we walk -- just if we walk down from the top you see we have made one division here which is previously collected samples and samples collected in the future. By that we mean -- and please my fellow subcommittee members jump in if I have made a mistake or inserted my opinion over the agreement since I was not here all of yesterday.

Previously collected samples are those samples

that are collected before we publish the report and before our recommendations have a chance to get in to effect. Samples collected in the future would be samples collected under recommendations that would modify the procedures currently used. We thought that there were important reasons to distinguish those two. In part, one does not want to throw away what we have -- the 200 plus million samples.

At one point in our deliberations we had divided samples collected for the purpose of clinical care, that is you go in for a biopsy for your care, from samples collected as part of a research study, part of N-HANES, the Physicians Health Study, the Nurses Health Study, whatever.

In our deliberations we began to see, I think, that those were not tenable, those distinctions, and that we should, in fact, collapse them and treat them the same, that whether the consent procedures were different, and in many cases they are different, the requirements that we would want to put into place, in fact, are the same or similar.

Then we made this distinction between those samples that are going to be used in an individually anonymous manner from those to be used so individual identification is possible. Initially we had the following

three-part distinction, actually four-part distinction: There was samples which are anonymous, Guthrie Cards; samples which could be made anonymized or anonymizable samples; samples which are potentially identifiable; and samples which are going to be used in an identified manner.

We have not found that distinction helpful because when one thinks through or when the subcommittee thought through the kinds of recommendations we would make under those categories, in fact, they collapsed into these. We thought one of the problems of the current debate was the fact that everyone was focused in on how the samples are stored rather than how they are going to be used because the key issue is not whether your sample is in a research study but linking the result with the name. That turned out to be the key potential where harm can occur. So the key issue is are you using the sample in an anonymous manner in this research study?

Then we made some distinctions here, which we have subsequently collapsed, and I am going to talk about that in the next frame, which is there are samples which we have collected. In the past this has been true where you are looking at individual samples, there is no community link, there is no link even in an anonymous fashion, you are just say looking randomly for colon cancer genes not in

an ethnic or racial or some other geographic group.

Because of genetics but not simply limited to genetics as we see in some of the kind of research studies we have looked at we could imagine that there could be circumstances where even if you collected the sample in a manner or the sample was individually anonymous there might be relevant items because of the kind of sample you use or because of the kind of sociodemographic information that might have implications for a community so we began to make distinctions between that kind of research which might have implications for a community but might not in our imagings be harmful and those which might be harmful.

As a result of yesterday's discussion these were -- these two were collapsed.

I do not know where I have the overhead.

(Slide.)

So I think we are at the stage, and since I was not fully part of that discussion, this is the current -- Sally, I apologize.

(Slide.)

This is the current operative model.

DR. GREIDER: Zeke, aren't we missing some boxes on the right-hand side?

DR. EMANUEL: No. I thought at our last

meeting, not yesterday's but the previous meeting, we had suggested that there was no distinction between the clinically relevant and the research but I would stand corrected. We have all the permutations here.

DR. GREIDER: My recollection was that was true for the previously collected samples but not for the future samples and maybe other people can let me know if -- other subcommittee members.

DR. EMANUEL: Your recollection is this.

(Slide.)

DR. GREIDER: Correct.

DR. EMANUEL: My recollection is at the very end of the previous meeting was that Steve Holtzman -- we had suggested -- well, we can go through it because the suggestion is that the distinctions here, the recommendations we are going to make are going to be no different and, therefore, should be collapsed but this is a work in progress.

DR. COX: Zeke, I would say at least -- although I was not at the meeting but having read things, the logic, the exact arguments that you make for collapsing them in the prospective or in the retrospective for me fit for the prospective too because if you can collapse them for the retrospective then why can't you collapse them for

the prospective so it does not make any sense to me not to collapse them.

DR. EMANUEL: Well, I think the way to understand that is to work through each of the boxes as the subcommittee did and the rationale for them. Let me emphasize what I think are the -- and I would hope that my fellow commissioners would again -- the three path breaking, I think, distinctions we have made. One is between the previously collected samples and the samples collected after the report's recommendations.

The second is that the evaluation, the ethical evaluation, should be based on the use of the tissue, not on the manner of collection or storage of the tissue, because what we are interested in, and the reasons we have worries is the harms that result and that depends upon being able to identify a specific result with a specific person, and that recognition that some research conducted on individually anonymous -- in an individually anonymous manner may nevertheless have sufficient sociodemographic information to adversely affect communities.

MR. CAPRON: Could you pause now because --

DR. EMANUEL: Well, let --

MR. CAPRON: -- because you think you have responded --

DR. EMANUEL: I want to -- can I --

(Slide.)

To put this a little bit in a framework the current system, the Common Rule, recognizes only two categories. All right. It has nothing to say about the rest of this. This is really the reason we are here and looking at it because it is solid on all these other boxes.

Now, I do not want to -- I do not know if the commission wants me to potentially jump ahead and suggest what the recommendations were or should we just leave that?

DR. MURRAY: I think we should go ahead.

DR. EMANUEL: Does that sound --

DR. MURRAY: Does anybody want to comment at this stage?

MR. CAPRON: Yes.

DR. MURRAY: To respond to Alex -- well, but I think -- okay.

MR. CAPRON: May I --

DR. MURRAY: Go ahead, Alex, have your say.

MR. CAPRON: Well, thank you.

I agree entirely with the notion of the focus being not on the way samples are stored but on how they are used. It seems to me that there is a self-evident distinction between a sample which has no identifiers and

those which have some information and are encrypted. There are two distinctions.

One, the information, although it may seem to the person who is making the decision at the time is sufficient to make it anonymous may not make it anonymous.

Secondly, after the fact a researcher with findings, which he or she regards as important enough, will have information which could be unencrypted. That is a fundamental distinction it seems to me and the whole notion that in certain research you need fire walls or you need one way barriers and the like because you have information which has an encrypted number on it, which if unencrypted, goes directly to an individual suggests that there is a distinction.

I do not think that what I have heard thus far explains to me why you want to lump those two together.

DR. EMANUEL: I think, Alex, the answer to that question is let's get through the protections we would like and see if, in fact, they collapse or they do not collapse. Right? That, I think, is the rationale that led us to collapsing them because, in fact, the kind of protections you would want, the kind of consent or IRB review that you would want for those two different categories, in fact, collapses them. They would be the same.

MR. CAPRON: I read your charts before this meeting. I came to a different conclusion.

It does not seem to me that I have the same sense about information being used where a person could have results of great importance to me which they could unencrypt and where there may be a moral obligation to do so in order to give me a warning or conversely where their scientific interest in unencrypting it is very different.

To have a sample used in advance seems to me does not fit under your -- the conclusion that you have given about no IRB review, no individual consent, no community consent in the same way as it would with a sample about which there is no individually identified linkage at all possible. Therefore, that is one of the reasons why it seems to me that different policies must be in place. Certainly the policies having to do with whether you could under any circumstances go back through that wall only applies to information for which the identifiers are there.

DR. MURRAY: That is not true. At least not in the hands of the researchers. The identifiers might be perhaps in the hands of a trustee of the tissue or even in an additional party, a third or fourth party.

MR. CAPRON: If there are no such identifiers you have no basis for going back. You do not need a policy

about not going back, right?

DR. MURRAY: Well, I think you are not hearing what we are trying to say here.

I also want to make a conceptual point, Alex, and that is if you talk to privacy experts, particularly for an issue like tissues, DNA samples, tissues containing DNA, there is not a bright line distinction between those samples that are wholly anonymous and those samples that are not. I mean, if I had access to DNA fingerprint databases then I might be able to link this particular sample even though every piece of otherwise identifying information has been stripped from it simply because I can do a DNA fingerprint from this tissue.

It is really a matter of how difficult it becomes to go back from what I have in my hands, from tissue sample with or without additional information, to a specific individual's identity. It is a continuum rather than a clear and bright line. I think that helps -- that helps me, at least, to think of it in that way.

So the question becomes what protections can we put in place that would reasonably assure that a person whose sample with or without other information has gone forward to a researcher and can count on that not being then subsequently identified.

MR. CAPRON: Well, obviously if a person has a sample, an anonymous or encrypted sample, from you and finds out information about it and then later gets another sample from you, a genetic fingerprint can indicate that you were the source of the first sample. I totally agree and that is something that raises a different issue about genetics. I totally agree but that is dependent upon that person getting another unencrypted sample.

DR. MURRAY: Get access to a state DNA fingerprint database. I mean, they are -- and privacy -- I mean, you probably know more about this literature than I do but privacy experts assure me that it is really a matter of how tightly you wish to protect it.

MR. CAPRON: Are you in the state DNA fingerprint bank at the moment, Tom?

DR. MURRAY: Not at the moment not that I am aware of.

MR. CAPRON: All right.

DR. MURRAY: But --

MR. CAPRON: So, in other words --

DR. MURRAY: I know your point but things will become more widely available in the future. I mean, we need to think not just where things are today but in the future.

Bernie wanted to say something.

DR. LO: I think one of the problems we are having is that we are trying to have a full debate in miniature and I think all these issues need to be -- all these issues need to be discussed and I think I just want to make two points. One, where we end up in our matrix may not be where we want to start. So at conception I think most people do come with the intuition that there are many, many more rows and columns than we may end up with.

I think as Zeke was suggesting it is only if we go through the arguments and find that a lot of the rows and columns are identical after deliberation. Do we then say the recommendations will collapse? But maybe as we present this we should start with the fuller matrix and argue through why it collapses down and obviously we cannot do that in an hour-and-fifteen minutes.

The other point is that, Alex, what you were saying about the importance in some situations of being able to deencrypt that information either for the purpose of reporting back to an individual patient, close but not there yet, to report back to an individual patient the findings that may be of clinical import to that patient. Or the other situation where that is likely -- that may come up is where the scientists wants to get back to that

patient because they have such an interest in genetic constellation they want it to be studied more.

Now whether we build that in to the model at the onset or have a simplified model which adds these in sort of as variations on policy I think we need to argue out but certainly we do not want to lose track of the points you were making, Alex, about how the fact that it is encrypted or presumably at least the possibility of unencrypting and there may be valid moral reasons for wanting to do that or compelling more reasons to do that in some situations.

Obviously you cannot do that if it was collected anonymously as opposed to collected with identifiers which are somehow stripped or coded but that is something we started to talk about yesterday and I think it is fair to say that we have not quite resolved that one.

DR. EMANUEL: Can I say something?

If you think through these boxes there are three and only three protections, I think, that you can have. In each of the boxes you can ask the question has an IRB reviewed the protocol.

I have never had a complaint about the volume of my voice.

You can ask the question has an IRB reviewed

the protocol, has the individual consented, and has the community in some way offered its consultation. Those are the three possibilities. If you just do the math you have got nine permutations. We have got more than nine boxes, which means that some of the boxes are going to overlap. That is just on a simple level.

I think by going through each of those boxes you are going to see that the -- I mean, your view of what the kind of protections you want may be different from my view but, in fact, there is going to be some collapse there. There has to be some collapse. We do not have other kinds of protections or we have not proposed a lot of other kinds of protections.

Now your moral intuition that these, in fact, initially look different is exactly why the commission, and I firmly believe why many of the other groups have come with making lots more divisions there, collected in an anonymous manner, you know, made anonymizable, et cetera. But, in fact, I mean again to reiterate I think we have come to the view because we have actually tried to work through the boxes and said, "Well, you know, the protection we think is appropriate here recognizing that there is going to be some trade offs, in fact, look the same in these two boxes and that they are not conceptually

distinct."

MR. CAPRON: Well, I will wait until we get to the point of looking at what the protections are.

DR. MURRAY: David?

DR. COX: Zeke, I think that you said that very nicely and in terms of what the motivations for the boxes were but perhaps the debate can be -- and, in fact, it is perhaps the reason why the other groups had more boxes is that they did not start with the premise that the only things that were available were those three things, those three types of protections.

Now certainly in practice those are the three types of protections that are existent today.

The question, I think, a third question to ask, is should we start with that premise and say that those are the three types of protections because there is not practically an option for other ones right now or should we say -- should we back up and say because things do not fit into these nine categories very clearly that we should have other types of protections as an initial starting point? I think that is a very important thing.

Certainly the subcommittee by signing on to the matrix did the former but if other members of the commission do not start with that assumption then it is

going to be confusing about why the matrix makes any sense.

DR. EMANUEL: Hold on. That I do not think is fair to the history of what happened, David. I mean, that suggests that somehow this is Zeke Emanuel foisting this and the rest are signing on.

This was a long debate of us trying to reason through what the protections are and those three, I should say, are not the three we have today. Let's be clear. We have two today. Community consultation exists no where in the Common Rule. We have individual consent and we have IRB review. We actually added permutations on those in terms of IRB administrative review, possibly a general consent as opposed to a specific consent, so we have been trying -- I think we have been trying to be innovative in the kind of requirements we are suggesting.

I think this has been a long process of deliberation, you know, and one of the problems of the subcommittee framework is the months of trying to think through and argue through by using examples, you know, the Physicians Health Study or the Angiogenesis Factor of Breast Cancer Women, or some of the other studies, the kind of reasoning that we have collectively come to is hard to, you know, recapture in a short succinct manner.

I mean, it may be, you know, if we want to

think of some research and test out in those boxes that may be the most effective way to get everyone at the same place.

DR. MURRAY: Bernie?

DR. LO: Since I am congenitally optimistic I would like to suggest I think this is actually a fruitful discussion. I mean, first of all, I think as we were talking yesterday about planning the outline and the drafts of the report, I think here we have clearly seen that we need to separate out our recommendations in terms of our final matrix from the intuitive matrix most people bring to this and to sort of lay out in an earlier chapter all the considerations that lead to different rows and columns which, I think, we intended to collapse down in the draft that we saw yesterday.

The second issue is one of maybe we should readdress the issue of are there other types of protections other than just IRB review, consent and individual consent and community consultation. I think there are other things out there that we should think about. One is sort of a national review body beyond IRB review, sort of a RAC model if you like, with all the pros and cons of that.

Secondly, we have played around with variations on IRB review and I think in addition to administration

review and full IRB review there may be categories that segregate out as exempt from IRB review because people have gone through enough studies to realize that these do not really require anything more than, you know, what now I think are termed exemptions under the Common Rule. But I think this discussion to me is valuable in that it makes me realize we need to articulate better the rationale for collapsing down the matrix in final recommendations and also forcing us to rethink are there other kinds of protections that would give us even more permutations for the different boxes.

DR. MURRAY: Harold and Larry?

DR. SHAPIRO: I have just a simple -- I think it is a pedagogical suggestion. It does not enter into the substance of this argument but I found it helpful and just pass it on.

I found it helpful in looking at these various possibilities and matrixes to organize it somewhat differently, which gave me more flexibility in my thinking, namely I would put along the top "possible protections," and they define all the rows. And then -- excuse me, they define the columns. Excuse me. They define the columns. And then down -- but to define the rows are just differences you would want to make, whether you want to use

the differences you have or additional ones, or add additional ones.

And that all will enable you to keep in front of you easily protections on one side type and type of experiment or something on this side.

You may or may not find that useful in dealing with this. I have found it useful in my own work now.

DR. MURRAY: Thanks.

Larry and Steve?

DR. MIIKE: I think the purpose of a body such as our's is to get down to the elemental considerations and then it is for others to put permutations on them. So, I mean, I think that is a fundamental reason why I would say that we want a simple model and then you argue about the distinctions between them.

So if we start with a matrix that is so complex that nobody can understand what the underlying basic rationale is we will never get anywhere but if you start -- but if you end up where we, as a subcommittee, currently are and then you can argue the permutations around that like Trish and I were doing I think it is clearer to others.

Then, finally, I think if I remember my math, the magic number is seven plus or minus two and most people

cannot remember anything beyond that. So we are in that magic circle right now.

DR. MURRAY: Steve?

DR. HOLTZMAN: I guess I have a very simple view of the point Alex is raising and thinking about our deliberations, and that is what we care about is the nature of the protections, the nature of the processes that will go along with the research being done or not being done.

So, Alex is simply pointing out something we started with as well, that there is a distinction between samples where it is logically impossible to connect them to an individual, samples where they are connected to the individual in the research and in between ones where it is physically difficult but not logically impossible.

The question -- where the rubber hits the road the question is are your protections different, are your processes different? We concluded that with respect to the logically impossible and physically very, very difficult the protections would be the same, the processes would be no different.

So, I guess, what I am saying, Larry, I would start with the more complex conceptual scheme because it is out there in the literature and explain why we have reduced.

I think there is a reasonable discussion to be had, and I think Alex wants to lead that, that says he feels either that there are three different processes, three different levels of protection, or he wants to collapse the physically difficult into the same as being identified.

MR. CAPRON: Tom?

DR. MURRAY: Alex?

MR. CAPRON: I think that is fair and I like Harold's way of going about it.

It seems to me that the matrix we are talking about is a three-dimensional matrix and the dimension that has not been mentioned so far is what risks is a person exposed to in any particular situation. What types of risks?

For example, the risk that someone knows something about me that I do not know and the risk that, therefore, I will come to harm, that was preventable if only I knew, or the risk that I will have a knock on the door with someone saying we would like now to get more information about your current health status because we have found something about you genetically that you did not know and we did not know until we did this study. Those are different situations.

As you say, there is a situation in which it is impossible and another situation in which it will happen, and another in between.

So it seems to me that it is not just talking about what the protections are but the reason to lead towards one protection or another is going to vary depending on what you see the risk is.

Let me follow this through in another way. I think I am persuaded by your decision as to previously collected samples to collapse those which were collected for clinical reasons and those which were collected for other research purposes, obviously not for the current research because otherwise it would be a prospective study. That is not the intuition I started with and it is not as though every division and every distinction I think of I follow through to suggest we have to show it.

The reason being is if you take that risk approach it seems to me it is very likely that the things that would concern people would be the same whether or not their tissue had been taken out as a result of a diagnostic or therapeutic procedure or some unconnected research and that is not the intuition I started with.

I should note, however, I think we need to address that with some care because in the first chapter in

giving the overview you note quite correctly that most people whose samples are among these hundreds of millions that are being stored do not know that those samples are stored because it was not an explicit part of the consent process and it was never focused on.

That is not true for people whose samples were taken for research. They at least know samples were taken for research, they do not know about this research, they may not know how long it is stored but at least they know that someone took it to study it. Now that is a distinction.

But if we look to the future and say not what I was originally concerned about, sort of the dignitary difference between having something done to a sample you do not even know anyone has versus the other, but what risks you are going to be exposed to. I can understand why you ended up collapsing those.

Just to show that I am not totally pigheaded, Tom, I can understand why.

But I do immediately when I think about the risks see differences so I will wait and see whether the collapsing that you have done, which apparently has been done as to future samples in different people's view.

I mean, Zeke thought you collapsed research

studies and other samples of the future.

Carol thought you had not and you were still keeping them separate.

So maybe even the committee is not quite clear where its matrix goes.

Certainly in looking at the materials that were distributed in advance I understand why Zeke came to that conclusion because it seemed to me that the 1b and 1c looked very much like 1e and 1f.

So I understand why that would have happened, Zeke.

But again there may in the end be there some difference in how we think about people knowingly encountering a risk. So I want us to -- when you lead us through this -- address this question of what different risks you thought were at issue and why you think that treating different types of study the same way is right and why these three levels of protection -- the third level by the way, of course, is in the CIOMS documents and so forth. It is not as though we thought up community consent but it is there.

There is that recent article that was in Nature Genetics that you have probably seen by Foster, et al., which addresses that process.

So, I mean, I think it is a worthwhile concept to bring in but I do not think that the fact that there are only "three types of protection" means that the level of risks that are involved are the same for all and, therefore, we would invoke the protections with the same expectations of need for using them.

DR. EMANUEL: I think, Alex, your suggestion about the three-dimensionality of the framework is absolutely right and that is why the boxes are, you know, in some sense -- while risk is an important consideration, the way you take care of risk, what you do about it, how you operationalize it in terms of protections, that is what we have put in.

So your thinking and my thinking are exactly parallel and I think what we are seeing here is the question of, in fact, when we think about the kinds of research that are going to fit into these different boxes what are the levels of risk that might be involved and part of the problem is at least at the moment we do not have actually concrete research studies.

One of the things the commission did do is to look at some of the studies that have existed that have worked with these kinds of samples and talked about what we thought some of the risks might be.

One of the problems we have is there is a big long future out there and it is very difficult for mere mortals, especially some of us who are very distant from the lab, to imagine everything that is out there and, also, imagine what might come about but we have to do our best.

Again, I do think that -- I mean, I would just mention that at the end here the idea of collapsing the -- in the future the clinical research and the research studies, I was the last hold out. Carol was the leader of that as I recall. You know, this is a work in progress.

I do not know what you want. Do you want to go through the recommendations or do you want to go through some of the other issues?

DR. MURRAY: I think the most -- in my view but I would invite the other subcommittee members, in my view the most important thing now is to sort of go through quickly the recommendations for the various conditions, the boxes.

How do the rest of you feel?

If we can do that -- that is the most important thing we can do. I want to also have some time to talk about the other issues, community consultation and whether -- under what circumstances you would ever walk back through this fire wall. I want to do that but I think we

can do that after the two visitors join us and give their talks.

Carol?

DR. GREIDER: I was just going to ask a question about which version are we going to go through. This discussion that we just had it sounds like we need to go through a more full matrix version rather than the mini-matrix version based on the discussion we just had.

DR. HOLTZMAN: I think we could go with the mini-matrix. I think we all know what the full matrix looks like and if we go to the mini-matrix as we articulate the recommendation we can say why we collapsed.

DR. MURRAY: I agree with Steve.

Zeke?

(Slide.)

DR. EMANUEL: I think this might be the most helpful matrix to look at for a framework.

DR. MURRAY: Right.

MR. CAPRON: Can you tell us where we find this in this so-called hard copy?

DR. EMANUEL: In your place.

MR. CAPRON: In today's --

DR. EMANUEL: Handed out today.

MR. CAPRON: -- handout as opposed to the stuff

that was in our book?

DR. EMANUEL: Yes.

DR. MURRAY: It should be this one.

MR. CAPRON: These pages are not numbered.

DR. EMANUEL: This one. Proposed -- it says proposed policy just like it says up there. And it has got -- because there are two things labeled and you will see that -- one -- what happened is that they have got a row collapsed.

MR. CAPRON: A row which I should point out is based on this risk differentiation.

DR. EMANUEL: Yes, of course, that is why we did it.

MR. CAPRON: Yes, exactly, right.

DR. EMANUEL: But that is exactly the way it should be. There was an assessment that these risks should be -- I do not want to speak because I was not there at the collapsing but as I understand it that the risks, in fact, were something that ought to be determined by the IRB and not prejudged but whatever. I mean, someone else could speak to it more intelligently.

DR. SHAPIRO: I think in community consultation.

DR. HOLTZMAN: Well, to Alex's point about a

third dimension about risk, it could have one of two components. The first has to do with the identifiability and I think what you have said, Zeke, correctly is if that is all you mean by risk the third dimension collapses entirely into what are the nature of your protections.

On the other hand, if you want to start making risk distinctions based on the nature of the research then you do have a third dimension where you might then start to make differences in the kinds of protections.

Why we collapsed the community from nonstigmatizing to stigmatizing is we made the determination that if a community is implicated that one ought not, other than by going to the community for consultation, prejudge whether or not it would be stigmatizing.

(Slide.)

DR. EMANUEL: Look at the box labeled "to be used in an individually anonymous manner" and "individual, no community linkage" for a second and let's -- my paradigm, and it is only my paradigm of the kind of study that this involves is to think about a paper that I passed out on tumor angiogenesis study where people at the Brigham hospital went to -- got samples of women who had breast cancer lumps removed five and ten years previously and were

then looking at a new -- not actually genetic test but a new kind of test to make predictions about who would have recurrence or who would die from their disease.

They took 104 samples completely anonymous -- I mean, to the researcher anonymous but obviously to the pathologist who drew them out and wanted to correlate clinical information with the tissue sample. So that is a paradogmatic case, I would think, of that box. There was no interest in identifying ethnic groups or racial groups or other groups.

Okay. So the question is these women did not consent to this research when they came in for their biopsy. They may have signed a general consent that their samples because it is a teaching hospital would be used for education and research purposes. So what kind of risk do they face and what kind of protections do we want to put into place was the question.

In the boxes you can see the recommendations that we are suggesting, that the IRB -- I mean, it should be said that under current proposal, under current Common Rule guidelines no IRB review for this necessary and no consent necessary. At least that is our interpretation of the guidelines.

MR. CAPRON: Could you explain one aspect of

the research?

The researcher here is the geneticist, is that right?

DR. EMANUEL: This actually turns out not to be a genetics study, which is I think relevant. Not all of the studies that should be -- I mean, we have not emphasized that but this does not only apply to the genetics.

MR. CAPRON: Right. But where genetics -- our task starting off with was to look at this from a genetics point of view. Let's try genetics for a second.

DR. GREIDER: We have debated that a lot.

MR. CAPRON: Who is doing the study? I mean, it is not the person who holds the samples.

DR. EMANUEL: That is the pathologist. No, it is a researcher, a separate researcher.

MR. CAPRON: A researcher. He or she is looking at the tissue sample for some reason?

DR. EMANUEL: Right.

MR. CAPRON: Right. And what he or she has done has gone to the colleague in pathology and said, "Can you send me 100 samples of women who came in and had biopsies taken and who had X, Y, Z disease," is that correct?

DR. EMANUEL: Yes, that is right.

MR. CAPRON: And he gets the 100 samples and they are labeled one to 100 and --

DR. EMANUEL: Right.

MR. CAPRON: -- and the pathologist does not keep a record of which people those came from.

DR. EMANUEL: Well, even if he does I mean we can play it through. But say he does keep a record for the most extreme case he keeps a personal record. I mean, one of the reasons for talking about the encryption barrier is to say that there is not -- you cannot walk backwards.

MR. CAPRON: Well, encryption -- with barriers you can walk backwards but if there is anonymous samples with just one to 100 and he does not keep it you cannot. I mean, if he later -- now what we are -- it does seem to me that the genetics aspect comes in here.

Suppose that what the researcher is doing is not asking for the medical record to find out about the sexual history or the gestational history of these women but is instead asking is there a gene here and he looks through these and he says, "In this group I get 88 of these women have a gene," and he goes out and he says to the pathologist, "Send me samples from 100 women who did not have this cancer." The pathologist sends them and he does

not find the gene in any of them.

Now at that point if the sample is totally anonymous and he says, "I have got to tell these women something," the pathologist will say, "Sorry, there is no way I can. I just sent those out to you. I put numbers on them. There is nothing you can do."

If he says to the pathologist, "I have got information that may be of relevance to those women and their sisters, and their daughters," and the pathologist says, "Oh, well, if that is really that is important I can -- we can tell those women to come in and see you because we have now found out which of them has this gene and they can then make contact or give us the names of people we should contact."

Now to me those are different situations. Facially obviously different. It is a whole different set of considerations that should come in.

DR. GREIDER: Can I make just one point, which is what you are also making -- not making and distinguishing -- is research and clinical care. Just because a researcher finds a particular mutation in the gene does not necessarily mean that becomes the norm in clinical care and that those people need to be told something because of one particular study.

MR. CAPRON: I realize that in the lab he has it is not a CLIO approved lab and the results may be inaccurate for that reason. I mean, I know the difference between --

DR. GREIDER: So the question is would you want to walk backwards under those circumstances?

MR. CAPRON: Exactly. In other words, I am not saying that the response should be to walk backwards. I am just saying that the possibility of having results which would cause the researcher either to say I want to know more about these women -- I mean, is it, in fact, this gene that I have found or is that the gene that causes them all to be great pianists.

What I am really looking at is the coincidence that they have that gene and they were all living in an area that got irradiated in the 1950's and no one realized it or they were all drinking the milk or, you know, whatever the reason or some other factor. I am looking at a totally spurious unconnected thing and I do not know it. I need to know more about those women.

So whether it is a therapeutic impulse on the researcher's part or a, gee, I need to know more about these women now to know whether this finding has any significance.

The answer in each case may be we have encrypted it and we have encrypted it for the reason that you should not have access and we are not going to give you access. That is a possibility. But we all know human nature and we know that there is at this point the potential to say there is a good enough reason to do that.

The situation is different in these two situations on the face of it between the encrypted and the totally anonymous cannot be linked, you know, you did not get anything other than the fact you got a sample that started off with a diagnosis in the category that you wanted to research.

DR. EMANUEL: But, Alex, I would go back -- I agree with you 100 percent. Facially they are different, right. One you have the potential if, in fact, you kept that sheet of what number one really means of going back or -- I mean, even if you actually ripped up the sheet if you are in a pathology department with enough work you could actually go back. It is not like you cannot go back just because you have ripped that sheet up.

So now the question is what kind of protections, Alex, would you like in place, how high do you think that risk is and what kind of protections do you think should be in place before you -- to do that study?

Now traditionally in this country we have said you do not need consent for that. It is an existing tissue. You do not have to have informed consent. That is what the Common Rule says.

If you get consent to go back to that 104 you may face lots of problems to do that kind of research and the longer back you want your samples,the more clinical follow-up, the more difficult it is going to be. People will die. People move. America is --

MR. CAPRON: Right.

DR. EMANUEL: It is a very difficult place as opposed to other countries.

MR. CAPRON: Right.

DR. EMANUEL: And the question you have, I think, is how high are the risks to these people, what kind of protections do you want to put in place, and while there is this temptation to go back and forth can you create a system, devise a system as we have been thinking about of encryption without going backwards or going backwards under certain procedures that satisfies you that, you know, you have lowered the risk to a reasonable level. You are not going to lower them to zero.

As Tom says, even with Guthrie Cards to the

future you may not lower anything to zero because we are all going to have our DNA sample on a micro chip.

MR. CAPRON: Well, then the question then is we are now talking about a protection that is not one of your three. It would be a protection that would say it shall be unlawful, it shall never be done, or it will say it shall never be done except when the following extreme circumstances are made out.

I mean, I assume your committee has talked about what that except when will be and I am eager to hear it. So, I mean, maybe we should at some point get to that point. But then we have a need -- in the category of something that is encrypted, we have a need for that policy. Because of that we are placing a person at risk that they will get information which they may not want or other people will have information which is potentially accessible to other third parties.

I mean, let's talk realistically about nothing is totally confidential here or we talking about the need in all of these things to talk about what problems will come to a researcher who does not keep the information which he has managed to make un-anonymous from others.

I mean, it is an enormous difference for a person then to learn that they are at a genetic risk which

they did not know they were at when they go to fill out their next life insurance policy. Have you ever been tested for X, Y, Z gene?

DR. MURRAY: Excuse me, Alex. I am just concerned about time. We actually -- the issues you are talking about right now are exactly the ones that we, ourselves, are wrestling with and want to talk about the circumstances under which, if ever, we would want to say there would be even a very rigorous procedure by which you would ask permission to go backwards and find out the identities of persons.

MR. CAPRON: You have not come up with --

DR. MURRAY: We have not made a firm and full decision. We are fully aware of the kinds of risks you have talked about but we -- I mean, we want to have you involved and everybody here involved in that conversation which Trish and Larry and others are going to lead but I want to do that a little after 10:00.

So if we could just allow Zeke to go through the rest of the boxes and the rationale for them.

MR. CAPRON: Fine.

DR. MURRAY: Thank you.

DR. EMANUEL: I mean, I think that you have a box here that sets a standard policy recognizing that there

may be exceptions. The issue is what is the standard operating policy without extraordinary circumstances?

Let me distinguish going down here in that first column from a situation where you might want to implicate a community or your research might want to implicate a community.

So, for example, you go through a Tay-Sachs bank where the samples were collected, you know, might now be completely anonymous, maybe the samples had no information but the results could have implications for a community. And in that situation we suggested -- again that is something actually the current regs do not recognize. We have made some suggestions here.

MR. CAPRON: You have gone through the word "consultation."

DR. MURRAY: That is the working term right now. I am sorry that "consent" even appears there but consultation is the current.

MR. CAPRON: That is good.

DR. MURRAY: Yes.

DR. EMANUEL: But what appears here is individual consent and community consultation.

MR. CAPRON: In the previous box.

DR. MURRAY: Yes.

DR. EMANUEL: Oh, I am sorry. I did not correct all of those. Sorry.

DR. HOLTZMAN: It is supposed to be community consultation.

DR. EMANUEL: Consultation, yes.

MR. CAPRON: Right.

DR. EMANUEL: I apologize.

The reason I did not do a search/find replace is because it also appears in the individual context.

DR. MURRAY: Yes.

DR. EMANUEL: We have distinguished these from cases where in the nature of the research you need individual identifiable -- so, for example, family pedigrees is the paradogmatic case in this situation or you have particular samples where you keep going back to a person and get either more sample or different kinds of sample, or do additional tests. So it is just an individual basis.

In those two cases the main -- the main difference here is full IRB review and full informed consent because it is potentially individually -- I mean, the researcher knows who that individual is. The researcher knows. It is done with a specific identification. Even in the family pedigree where all you

know is daughter number five, you know, daughter five-years-old, you have the potential to clearly identify them. That is the previously collected samples. The ones in storage now either from research or from clinical care.

Now the future offers us opportunities --

Sorry, Steve.

DR. HOLTZMAN: Can I just take one step back?

DR. EMANUEL: Yes, please.

DR. HOLTZMAN: Just to explicate some of our reasoning. We did start by saying with respect to extant samples that maybe there was an in principle distinction between those collected and the research context of those versus those collected in the clinical context. So we then asked ourselves so how would that play out and why would it be different, and I do not have to rehearse the arguments for even why they are different.

But what we concluded was that the collection in the clinical context there was essentially no consent for future research. In the context of collection in a research context, even though they had agreed to engage in a research enterprise, they had not engaged in the consent of future research enterprises which were not envisaged and so that was morally no different than having not consented.

So, therefore, we collapsed those together and

said, "What are the levels of inappropriate consent that would be important?" We said, "With respect to if it is anonymized that no consent was necessary because there was not the potential for harm." I am not going to get into about the wronging aspect here. I am just stating the conclusions.

And that with respect to if it was going to be research in which they would be identified consent was necessary because even if there had been a general consent to future research it was not logically possible to have been an informed consent because they could not have made an assessment of the risks, harms, benefits, et cetera, to research that had not been envisaged.

DR. EMANUEL: Thank you. That was excellent.

In the future the main difference is that we can change the consent process for clinical collection as well as research collection and these are not settled categories as you heard.

But if you talk about situations where people are coming in for clinical care and there is no plan or known research to be associated, again we could divide these into two different categories. I think generally one should identify that any time you are going to -- any situation where the individual is going to be identified we

have agreed there should be full informed consent or potentially identified, even if in the results they are not going to be identified, but if someone could walk back either because it is a rare disease or the way the pedigree is laid out.

Two, samples that are to be used in an individually anonymous manner, the issue here is what kind of individual consent should there be. And out there in the debate there are some people who want the current system, no consent or the one line that is in the sort of general consent when you come into a hospital. There are some people who want a full informed consent down to, you know, I give permission to this specific researcher to do this study but to no one else.

Contrary to what is written here I think our general view is there should be a general consent for research or a general consent to have their stuff not for research. We have tried to work through some general -- what those consent forms would look like and I think, in general, they turn out to be very difficult. The one we have from the Breast Cancer Coalition is specific to breast cancer. The problem is if you try to make it more general for anyone coming into the hospital or something like that you find some difficulty.

DR. MURRAY: Zeke, can I make just one point that would go for all of the -- particularly the ones collected in terms of clinical care?

DR. EMANUEL: Right.

DR. MURRAY: Whether previously or now. If there is on the record that a person did not want their tissue used for research that preempts any possible use. We do not -- we did not specifically note that in this table but that should be noted.

DR. EMANUEL: The other thing to note is that we heard from Bartha Knopers that in Europe or at least in the Netherlands they were going to a presumed consent with an opt out. For our reasons we had thought and discussed why that might not be good and it might encourage sloppy record keeping if you could not identify a record and other reasons.

So I think, in general, we are moving to having the general consent process and we had thought through some of the problems and difficulties because we had heard from some of the people in our mini-hearings about the fact that they do not remember even signing a consent form and they felt coerced, et cetera.

Now without going through each of the boxes, I mean we can again try to discuss --

MR. CAPRON: How does the general differ from the present situation? That is to say -- you know, the assumption is when I went into the hospital last year I signed a consent form that allowed general use of tissues. I mean, there was some language that was not brought to my attention but it was there.

Is that what you are thinking about?

DR. EMANUEL: No.

MR. CAPRON: You are thinking about something that goes well beyond that. In practical effect --

DR. EMANUEL: Let's say -- let's be clear. One of the reasons we are not going to full informed consent is because in many circumstances when you collect your tissue you --

MR. CAPRON: You do not know what the study will be.

DR. EMANUEL: We have no idea what the study -- and we do not want to tie hands today for studies that might -- we might want to do fifty years from now or whatever. So the issue is what kind of consent can you have? Is signing a piece of paper where there is one obscure line -- and actually some of us have looked at some of those lines. They are not nearly as good as you would like them to be currently. So one issue is to make that

much more explicit to people to bring it to their attention to think about ways in which they might be alerted.

The other question is what kind of check offs or limitations can people provide? Wanting to be recontacted for future involvement in studies. Wanting to limit it to certain diseases.

DR. MURRAY: Right.

Steve and David?

DR. HOLTZMAN: Just to walk through a little bit of the thinking and here it may be more my thinking than the subcommittee's, I think.

I start in the research studies box of tissue to be used in the future in an anonymized manner. There is the case where we are not saying you just get a -- it is -- since you are in a context of a researcher describing the specific research the question is whether or not you can get an open ended consent to future at this point unenvisaged studies.

DR. EMANUEL: Yes.

DR. HOLTZMAN: Some have argued in the literature that that cannot be informed consent so, therefore, you should not be able to do it. You can only use the sample for a certain study and then you have to go throw it out, et cetera.

I think what we concluded was that it would elicit to obtain such an open ended general consent to research in conjunction with the specific consent to the specific research provided that that open ended referred to future studies conducted in an anonymized manner.

Okay. So that is how that box comes about so even though it says general what we mean is the specific study consent plus an open ended general consent with the opportunity there to say but not research of this nature or not research of that, that it cannot be given to a commercial firm, it cannot be used for whatever because you are in a research context.

So the question about collapsing them is now when you look at that which is collected in the clinical context clearly there is no research protocol you are describing. All right. The principle of if there can be general consent to open ended studies is on the table. All right. We think it can be. All right. We think provided again that it is conducted in an anonymized fashion.

The question then becomes to some extent a pragmatic question about what level of detailed and consent one can engage in and should engage in, in the clinical context where we have heard much discussion about being sensitive to the patient. All right. That is the last

thing on their mind when they are going into the biopsy is about research. And weighing the -- let me call it autonomy rights of the individual which we give very robustly and fully when they are in the calm atmosphere of a research context versus when they come into the clinic and weighing that against the potential for those samples just not being available whatsoever.

I think that is what we struggled with here about whether or not to collapse.

DR. MURRAY: Thank you, Steve. That was very helpful.

DR. COX: So to go one step further that was the reasoning. So in my simple minded way what is the punch line? Zeke has filled in the boxes so what is the punch line, big picture punch line if we look at those boxes. First we have a ton of samples that were previously collected. Can we use them or not? Can we say -- okay, even though those were not -- and that is both from the point of view of research and from the point of view of the clinic, the -- if we are going to use them with identifiers we have got to go back and get consent, full consent. If we are not going to use them with identifiers, okay, it is okay to use them even though we do not have the consent

right now. That is what we are saying. Plus or minus the community interest.

What about in the future? What is different about the future? There is only one thing different because using it with identifiers is no different whether we are doing it in the future or we are doing it later. We have not addressed using things with identifiers. Okay. Because we have not -- we have addressed it but we have not made any distinction. The only distinction is in the future if we are going to use things anonymously, okay, we get a general consent from people.

We get that general consent whether they are in research or whether they are clinical.

So what we have done is said the thing that is different in the future right now is that the Genetics Subcommittee is coming down as saying that we agree that there should be some general consent even if things are being used anonymously.

What we have not done, okay, is changed anything about the status quo from the status quo of things that are being used with identifiers. That is the way I read the way the boxes are filled in and what the summary is.

DR. MURRAY: Zeke, do you want to respond to

that? It is 9:30 and we are supposed to go to the next item but I want to give you a word here.

DR. EMANUEL: I think that the -- I mean, there is a balance here and what -- I think David's general picture is right but we recognize that there are going to be some exceptions and tough cases. The one of you find something either serendipitously about someone and you might want to walk backwards. How -- there is also the policy issue of how detailed that encryption or how that rigorous that encryption barrier is. And I think those are important issues.

We are trying to create a workable policy again which can be implemented by IRB's throughout the country and -- because I think realistically we are not going to have -- these are not the kinds of studies that you are going to have a RAC-like -- because there are going to be hundreds of them throughout -- if not thousands of them throughout the country.

We also -- I think my final comment is we need to -- while genetics is here everywhere, I think my own reading is there are going to be just as many studies that are not genetic and we need to be very clear about that. There are a lot of immunology studies. There are a lot of studies of new factors that are not at all genetic. So we

need to be concerned about -- in some sense the genetic ones raise some issues because you can have a genetic fingerprint but the policy has to be broad to cover all the items.

Now, I mean it may be a worthwhile intellectual exercise to say let's look at the Guthrie Cards and let's look at the pathological samples.

What are the kind of different protections you would like, Alex, or you think might be in place there? Would you -- and here is where -- would you in the pathological -- in the case of the pathology samples want to have full consent because -- on existing pathology samples because that is what I think would be required?

I would just say that in my reading of the literature no one has suggested that.

MR. CAPRON: Why isn't that a matter of the choice of the subject? In other words, looking at the breast cancer documents and the --

DR. EMANUEL: In existing samples?

MR. CAPRON: No, not existing samples. Excuse me. Future samples.

DR. EMANUEL: But that is what we were talking about. In existing samples --

MR. CAPRON: The existing -- you had moved

forward to the --

DR. EMANUEL: Well, you raised the objection in the existing samples first. So let's just talk about the existing samples. I am going -- I have a pathology lab. It has got hundreds of thousands of samples.

MR. CAPRON: I would say those can only be provided on a truly anonymous basis.

DR. EMANUEL: I ask you what does truly anonymous mean to you separate from the --

MR. CAPRON: It is not encrypted. Anonymous. It means that there is -- that you are getting samples that --

DR. MURRAY: Could sex go forward?

MR. CAPRON: Excuse me.

DR. MURRAY: Male or female?

DR. EMANUEL: Could any clinical information be attached to the sample?

DR. MURRAY: Age? Or could go nothing when you said nothing?

MR. CAPRON: I would say that if there is a clinical category --

DR. MURRAY: Disease.

MR. CAPRON: -- and you are asking for a group of samples of males or females or people within a certain

age range you can get a group of those samples but among the samples individually there is no encryption.

DR. MURRAY: We are going to have to come back to this because I think I disagree pretty strenuously.

DR. EMANUEL: I am not sure what you mean. I am not sure what you mean by --

MR. CAPRON: Your example of the 108 breast cancer or whatever samples.

DR. EMANUEL: Yes.

MR. CAPRON: All that you wanted was send me your breast cancer --

DR. EMANUEL: No, no. With attached clinical information but not identifiers. That is what we are distinguishing. No social security, no birth date, but age, clinical course -- whether the -- I mean the essential information being whether the cancer recurred or not.

DR. MURRAY: I think we just need to think about this one because we will come back to this but I do not -- we have guests here and I do want to -- we have to let our guests speak and I have a feeling the issues will come up as they speak so it is not like we are completely suspending this conversation.

I know Rhetaugh had her hand up and I want to give her the last word now and then we are going to turn to

Dr. Old.

DR. DUMAS: I think I might be missing something but my lack of understanding might be useful in this case. It seems to me our basic principle is informed consent and if we have existing samples and it is possible to obtain informed consent isn't the question how to obtain that consent and if there is no way to obtain informed consent then there needs to be some statement about exceptions. Am I missing the point here?

DR. MURRAY: Well --

MR. CAPRON: The exception is that they want to be able to use the samples without any consent.

DR. DUMAS: Well, if it is not possible to get the consent but I am not hearing that the basic over arching principle is informed consent. And either you are able to get it or you are not. Now if you are not able to get it then you have to talk about the conditions under which you would be able to use the sample.

DR. EMANUEL: Well, let me say I think informed consent for some research studies -- one of the reasons we made the distinction between using it in an anonymous manner and used in a potentially identifiable manner is that in an anonymous manner you are not linking a result with the person's sample.

The second thing is the issue here is it is impossible to identify the person or is it possible. This again is going to be a big spectrum. The question is how much effort is necessary to do that? Remember in this -- many of these people will already be dead. Many of these people -- you know, 20 percent of Americans move every year. Outside of a research setting where you are tracking them for some reason it is enormously difficult and you are not interested in the particular person.

I would also say, Alex, on your remark it is not us. I mean, the current policy is no consent. Let's be --

DR. DUMAS: No consent?

DR. EMANUEL: That is the current policy.

DR. DUMAS: All right. Well, then --

DR. EMANUEL: Because this is existing data.

DR. DUMAS: All right. And I will hold my comments because we are going to talk about this again but I really would urge that we put as our primary focal point informed consent and how to obtain it.

DR. MURRAY: Steve?

This is going to be the last comment from a commissioner before we move to Dr. Old.

Steve?

DR. HOLTZMAN: Just to maybe lay out a little of the thinking here. This is not necessarily the subcommittee's thinking. I think it is general thinking about informed consent. Clearly if you can have it reasonably happen you want to get it.

Then the question is why is informed consent important? There may be two elements to that. Simplistically the autonomy right of the individual as well as the protection and the potential harms to the individual and so then when you look at the extant samples, all right, you then ask the question pragmatically the value to society of doing research versus the cost and difficulty of going back and getting the consent and that if you protect them against harm by anonymization or conducting the study in an anonymous manner, all right, that that protection against harm plus the value to society outweighs the autonomy interest. I mean, bottom line I think that is the argument.

DR. DUMAS: I think you are getting to the whole issue of who makes that decision.

DR. HOLTZMAN: All right.

DR. MURRAY: Dr. Susan Old has joined us.

Thank you for your patience and thank you very much for taking some time this morning to come speak with

us.

DR. OLD: Well, thank you very much for having me here and participating in this lively discussion.

DR. MURRAY: You are going to be asked to move the microphone -- pretend you are a rock start and have that thing in right in front of you. Okay. Thank you.

DR. OLD: Is it okay? I think it is going all right.

I am here today to talk with you about how the National Heart, Lung and Blood Institute at the NIH is grappling with some of these same issues. I believe you have all received a copy of our report from our Special Emphasis Panel.

So over the last several years the National Heart, Lung and Blood Institute, or the NHLBI as we are usually called, has become increasingly aware of extensive resources we have in our clinical and our population studies.

The NHLBI is supporting a large number of population studies for a very long period of time where stored samples have been collected and also future research down the road and so what we were very interested in is how can we use these stored samples and how do we construct

future studies to provide the widest opportunity of use of these samples for the public good and furthering public health.

So with the progress of the Human Genome Project, both in terms of some of the resources it is developing and some of the analytical tools it is developing, our population studies and our clinical studies, the samples from these studies are becoming increasingly valuable and very highly sought after.

So one of our goals was to -- how do we take the biggest advantage of these samples. What are the opportunities out there for using these samples and what are the obstacles to using these samples that NHLBI has stored along with also how do we do future research?

So the NHLBI convened a special emphasis panel called the "Opportunities and Obstacles to Genetic Research in NHLBI Clinical Studies." This panel consisted of a large number of individuals involved in various aspects of research and you can see the roster in the back. It covers all the participants -- all the various interest groups involved in collecting samples and using samples.

The guiding principles of this panel were provide the NHLBI with feasible, implementable, recommendations to supporting genetic research in these

samples, to take into consideration all the various aspects involved in using these samples. In other words, the various interest groups, the participants in studies, the investigators that collect the samples, and the public good. And then also the goal -- one of the goals was to use a carrot not a stick to help people share these resources.

It says right here in the overview one of the key issues is how can NHLBI's valuable data and sample collection be made available to the broadest scientific community while maintaining the privacy and the trust of the study participant and what barriers exist, either funding, samples, control, and how can they be overcome.

So this committee identified four key areas on how to make samples widely available to the community, disseminating information, getting information out there on an NHLBI studies, what studies do we have available that people could use samples from, how do we ensure that there are adequate DNA resources, in other words establishing immortalization and repository services to use these samples, facilitating collaborations and putting in all small grants to share resources, to further pilot studies, to get collaborations set up, and also protecting human subjects, and that is what I am going to be addressing

mostly obviously with this group today.

So the protecting human subjects section of the report starts on page 13 and as this committee has done the panel broke the discussion down into the two areas, prospective studies and retrospective studies. In other words, studies that the samples have already been collected or they are ongoing-ly being collected in our longitudinal studies, and in the future, studies that have not actually started yet and how do we deal with those sort of things.

So the panel thought that there would be major benefit to the individuals and to the public by facilitating research on stored samples so that there is where they started with their premises. How do we facilitate using these stored samples and how to go about doing that?

And that the policy should be based on the premise that there is major potential benefit to the public and this must be weighed very carefully against the risks to the individuals who do volunteer for these studies, and here I am talking mostly about research, not about clinical samples, although that does happen obviously in some of our studies where we have lung reduction studies or that sort of thing where you do end up getting pathological tissues but mostly it is based on our long-term epidemiological

studies and our clinical trials where blood samples are being stored for biochemical analysis and how do we change that into doing genetic analysis. How do we move this forward.

So just to jump to the punch line, and how this panel recommended, was that for ongoing incompleted studies or retrospective studies on stored samples that the NHLBI should encourage sharing anonymous or anonymized specimens and we use the definitions from the American Society of Human Genetics, anonymized -- anonymous means that they were collected with no identifiers to start with. Anonymous means that the identifiers have been cut and cannot go back.

These samples should be shared in this fashion, anonymous or anonymized, in studies where the study -- the new study is broadly related to the consent that the original participants signed. So, in other words, we have large studies where we are looking at heart disease and so somebody else who would like to use these samples to do genetics of heart disease they could be shared in an anonymous fashion.

Now if the new investigators decide that they would like to use these samples but they would like to get more information from the participant or they would like to

know something about the participant or that the result that they are going to get might impact and they would like to eventually go back then they would need to put their proposal to the IRB and to -- if they needed to use samples to do a new study where it was not specifically stated in the original informed consent where a lot of our epidemiological studies in stored samples do not have genetic consent.

So you want to go -- if you need identifiers -- and one of the reasons you might need identifiers is that let's say you collected studies to do hypertension and now you want to look at renal disease because it is related to hypertension. So that can be considered broadly related. But let's say you wanted to look at pulmonary function and that is not really considered broadly related, you would need to go back to your IRB. Okay. So that is why you might want to go back.

Now for the new studies the informed consent should be obtained for all new studies whether they are intended to do genetics or not, or clinical trials, or epidemiological studies, should be obtained to facilitate doing future genetic studies whether it is anticipated or not just to allow the door to be opened. And that these informed consent documents should be organized in a layered

fashion and this is outlined on page 16 on how exactly what they mean by a layered consent.

Essentially in the first consent that a person agrees to is to do the parent study, do the study on hypertension. This is we are going to do a genetic study on a hypertension. The next layer is to do broadly related research related to hypertension. We want to look at obesity. We want to look at stroke. We want to look at renal disease. These are all related to end stages of hypertension. And then the final layer of consent would be to do essentially the broadest possible anything. Now the participant obviously has the right to say, yes, I agree to the current study but I do not want you to look at stroke or I do not want you to look at cancer, or I do not want you to look at mental disease, and can backtrack, and then that would be part of the data file of what can be done with the sample.

All the way through in each part of the layered consent the participant agrees the samples to be stored, to be done, each one of the parts, and to be recontacted, which I think is an important part especially if you decide to send it on anonymously or you decide to have a new collaborator come in to do something identified, you want to be able to go back and get a new consent from the

individuals.

And then the final recommendation is NHLBI provide an example of what a layered informed consent would be and make that widely available and put it on the web or something like that so that investigators could use that to start the process of writing their informed consents for their future studies to go before the IRB.

I would like to say that these recommendations were put forward in, you know, agreement by this diversity of people involved in all the different aspects of research being genetic or epidemiological, or lab, or ethics, and also this document was circulated to our investigators involved in our large community and clinical trial population studies, and especially with those who have an emphasis in minority and under represented populations, and so this was seen in draft copy by a large number of people and it did come back that this was an appropriate direction to go into.

We have also begun to implement this layer of informed consent approach. In several of our studies we have an ongoing hypertension study that uses a layer of informed consent and some of our longitudinal studies such as Framingham is going back and instituting in their next cycle a layered informed consent. We have not had any

barriers to this. It has not been deemed that this is too difficult for people to get through this. I think when people are given the choice of what they are doing they are much more open and much more interested in participating in genetic research.

So I will -- I can talk about part of the report or focus on anything I have just said.

DR. MURRAY: I see Zeke, Harold and Carol.

DR. EMANUEL: And Bernie.

DR. MURRAY: Bernie. This is Zeke. I see Zeke but Bernie was the one who wanted to speak. Sorry.

Bernie?

DR. LO: It is the first time Zeke and I have ever been misidentified.

DR. EMANUEL: It must be those genetics.

DR. LO: I wanted to thank you for coming and also thank the NHLBI for doing this. I have a couple of questions that relate to the issues that this commission is talking about. First, on page 15 you say in the bottom sentence, "The advisory board investigators should seek advice about consent issues from members of the group whose tissue is being studied."

We are discussing sort of a more robust concept of community participation where it is not just "should"

but "must," and it is not just seeking advice but actually having representatives of the people who are going to be studied participate in the design, planning and actually be part of the steering committee or whatever.

So my first question is if you could discuss with us sort of exactly how much participation you thought was desirable and useful.

DR. OLD: Sure.

DR. LO: The second issue has to do with the consent for new prospective studies. I like very much the layered approach and the idea that we should try and make it work and see what works and what does not but err on the side of giving people more choices rather than fewer. However, I am concerned that we are putting again so much emphasis on the consent document, the form, and not on the process of discussion, and I think, you know, with the successful large prospective trials it is a relationship, it is a process, it is not a consent form. I am wondering how we can sort of get away from our obsession with getting the words right on the page to really getting investigators in studies out to talk to patients in ways that they will understand, which is, you know, just a lot harder than getting a model form on the web which everyone can copy but that is not the same as the consent process.

DR. OLD: No, you are right.

Let me go to your first point and that is community involvement. NHLBI has in the past for our epidemiological studies has large participation from community involvement. We have a Strong Heart Study which is with the American Indians and they are part of the steering committee. They are part of the process of deciding protocols. They are very active participants and I think one of the reasons that this is in here is due to having special communities like that involved already in our epidemiological studies. We expect them to have also input in our genetic studies.

We are currently in the process of setting up a study exclusively in African Americans in cardiovascular disease. They are also part of the process of defining the protocols, the study cohort, and on the steering committee. So NHLBI has already taken that step in terms of including the community in setting up a study and involvement.

I think on some of our studies where we are looking at a much -- we deal pretty much exclusively with complex diseases on -- not exclusively but a large number or things that are complex diseases and who exactly is the community of people with hypertension and where do you go to get community involvement and how do you study

hypertension, and in trying to determine the genetics of complex diseases you need to look at vast numbers of people, you know, if you are looking at any sort of asthma, any sort of large disease that you are talking about huge networks of investigators spread out all over the country and all over the world as it is and sometimes defining what the community is, is difficult.

They also recognize that doing just your standard epidemiological studies you could -- the results that come out of those put individuals at risk. You find that African Americans have higher rates of salt induced hypertension. You find that women -- men get heart disease faster than women, that there are -- the community can be women and the community can be men so in those sorts of sense it is difficult but where they are identifiable communities we do already seek input.

The consent form, the layered approach, I think that by having a layered approach at least what we have found in the current study where it is being used it does require a much greater deal of interaction between the clinic staff and the participant because you are getting something that they have never seen before. And in a large number of our studies we are recontacting, we are bringing -- you know, we have somebody from Framingham coming back

to do the Family Heart Study that is now in hypertension, you know. These people are being used over and over again. They have seen these things a lot. This is new and so they do ask and I have been in clinic site visits where they sit down and they are discussed.

I think that what this might come out of is that there is the perception that if you do not get everything down in writing you cannot do anything. So I think that is why there is so much information but I think that the idea is this provides the stepping stone for interaction between a clinic staff member and a participant.

DR. MURRAY: Diane, you had -- is this a direct follow-up or will it be quick?

DR. SCOTT-JONES: This is just a quick request. Could you send us a report of your efforts to involve the ethnic communities that you mentioned, the Native Americans and the African-Americans in those particular studies.

DR. OLD: Steering committee meeting minutes or I am not sure what exactly you would --

DR. SCOTT-JONES: Just anything that would give us a good sense of how you --

DR. OLD: How you do it.

DR. SCOTT-JONES: -- accomplished it.

DR. MURRAY: Right.

Harold was next.

DR. SHAPIRO: Just a small clarifying question. The question of your recommendations on page 15 dealing with retrospective samples. It was not clear to me and I apologize, you may have said this and I may not have read this quite carefully, not yet, that if -- excuse me. It was not clear to me if there were any circumstances that required new consent forms for -- or new consent, new individual consent for material from retrospective studies. I know they have to recontact IRB's under certain situations and they may have to recontact people if they are identifiable and so on. But is there any further requirement under these recommendations for a new consent?

DR. OLD: These requirements do not specifically say that. What they say is go back to the IRB and presumably the IRB would say to do this study you would need a new consent.

DR. SHAPIRO: So that is up to the IRB according to this.

DR. OLD: But certainly the NHLBI cannot -- it is controlled at the level of the IRB. It is not at the government level. But --

DR. SHAPIRO: Thank you.

DR. MURRAY: Let me tell you the plan right now. I have Carol, Steve and Zeke is indicating a desire to speak or to ask questions of Dr. Old. We had a break scheduled for about 10:10. I think we should try to take that if Patricia Barr is willing to be the first speaker after the break. So that is the plan.

Carol?

DR. GREIDER: I think that Bernie asked most of the questions that I had regarding the involvement of community although another question that I had was regarding your layered consent form. I am wondering whether the issue of research versus clinical came up there with regard to how practical it is to get a very detailed layer of consent in a clinical situation as opposed to in a research situation. In research situations you can sit down and talk to the person, et cetera. Did that issue come up?

DR. OLD: No. It was discussed specifically for research. It was how to facilitate research and to do genetic studies.

DR. GREIDER: Although you did mention that some of the samples do come from the clinic.

DR. OLD: The majority of the new studies that we would envision being set up to be part of this would be

a research although there is nothing to say that it could not be attempted in a clinical situation to get some sort of layered approach. It is not really a very complicated thing. It looks complicated and it sounds complicated, and in practice it has not -- we have not had anyone refuse anything or have any problems with it and it has been in effect for a couple of years now.

DR. MURRAY: Steve?

DR. HOLTZMAN: I would like to just try to focus then if I can on where I think -- I would like to focus if possible on where I think your recommendations are similar to what we have said and where they are different, and maybe try to elicit the differences in thinking.

With respect to the prospectively collected samples I believe we are very, very similar in our thinking at least with respect to those which are collected in a research context leaving open whether we think those collected in a clinical context can have such a robust consent process.

With respect to the extant samples you have focused on the sample being anonymous or anonymized versus our focus on the research being conducted anonymously or encrypted, what you call identifiable using the ASHG categories.

You also make a distinction between broadly related research versus any research. We did not make that distinction. We said if research could be done in an anonymous fashion -- let's forget about that for the moment even anonymously -- any research. We did not think that it required that it be broadly related.

You have not said -- as I think you have answered the question -- you have not said if it fails to meet these conditions therefore go to a consent process. You have said go to an IRB. All right. Arguably what they would come back with is go to a consent process or maybe something different.

Then the last thing that is -- I want to try to understand this and maybe how you are thinking, take something like the large epidemiological studies you support, Framingham, et cetera, et cetera, it is in the nature of those studies that the samples have to be identifiable because they are longitudinal studies. You are continuing to collect information. So that effectively what we proposed or was suggested is that if someone wants to undertake a study using Framingham samples and they are encrypted we could go ahead and do that without individual consent.

According to you, your suggestion here, the

Framingham samples could not be used in an encrypted fashion, all right -- no, I should not say that -- you would have to go to the IRB because in their very nature they are not anonymized.

DR. OLD: Yes.

DR. GREIDER: Okay.

DR. OLD: Going back a little bit, I think that the approach that this group took was how do we get these samples used. This was the baseline, was if the samples can be used how can we use them and they do say in here, you know, if it says in the informed consent they are to be destroyed this does not pertain at all so you cannot do research period whether it is genetic or not.

DR. HOLTZMAN: And that was the backdrop -- it is a backdrop assumption for us as well.

DR. OLD: Right. And so -- but I think that the underlying premise of this is that somebody has done a study somewhere on these samples, Framingham, Eric Strongheart, Honolulu Heart, they are sitting there somewhere. Somebody has done a study of nongenetics or something and now somebody wants to come in and do something genetic. And so the -- obviously the parent study has identifiers. They are doing their study.

But the new person coming in, whether they are

willing to do, you know, look at the frequency of some allele in some certain population, they do not need identifiers, but if they want to come in and they want to find in this, that and this certain polymorphisms they will probably need identifiers. They would have to go back to the IRB with a whole new proposal and it would be up to the new study coming in to the parent study -- now the parent study does not lose their identifiers. I mean, these samples are identifiable because they are for a research study but the new study coming in would either obtain identifiers or they would be anonymous depending on what their proposal is and then how do they proceed.

DR. HOLTZMAN: We need to be very clear on that. Now if the Framingham -- at least my understanding is the Framingham samples are not anonymized. If I come in and say I would like to use those samples, all right, I do not care about having identifiers. Even with respect to my use those identifiers are stripped.

DR. OLD: With respect to your use.

DR. HOLTZMAN: My use.

DR. OLD: Right.

DR. HOLTZMAN: Okay.

DR. OLD: You would have no --

DR. HOLTZMAN: All right. So in your

conceptual framework are those anonymized?

DR. OLD: Those are anonymized.

DR. HOLTZMAN: Okay.

DR. OLD: They are not anonymous. They are anonymized.

DR. HOLTZMAN: All right. So even though it is in principle possible to go back?

DR. OLD: It has to do with your discussion already this morning of how high is that wall.

DR. HOLTZMAN: Okay. So --

DR. OLD: Yes.

DR. HOLTZMAN: -- I think that is important because we are not being clear then in our distinctions, right, because you now go to where you took the distinctions, right, which are from the American society, right --

DR. OLD: Right.

DR. HOLTZMAN: It is on page 13, right. Anonymized were initially identified but had been irreversibly stripped of all identifiers or impossible to link to their source versus identifiable which is what we call research conducted anonymously or in an encrypted fashion. All right.

DR. OLD: But I do believe that this committee

assumed anonymized was as it was being passed on, that it was not -- the stored samples were not anonymized, the new study was anonymized.

MR. CAPRON: But they would have to encrypt it.

DR. OLD: It is encrypted and there are -- we have a variety of ways where you pass it through several number codes and you end up with one and then you throw away the thing in the middle and then you cannot go back because you have got three layers of number codes to get through.

DR. COX: Steve, the distinction with respect to our subcommittee is that these were anonymized but the researcher cannot go back, okay, as opposed to encrypted, okay, where the research, okay, does not know.

DR. OLD: Right.

DR. COX: But it is possible to go back.

DR. EMANUEL: No, no.

DR. OLD: And I would say encrypted is identifiable.

DR. EMANUEL: That is not true, David. It depends -- critically -- this is an encrypted sample. The question is what kind of encryption you have.

DR. COX: It is an encryption so that the researcher cannot go back and no one can go back.

DR. HOLTZMAN: So I think we need to be -- you know, as we look --

MR. CAPRON: The term of art is anonymized.

DR. HOLTZMAN: Well, okay. So as we went through our discussion before we got to the issue of the researcher being able to go back, for clinical purposes let me call that, that you made a discovery should you be able to go back to the patient and help them. Before we even got to that whole issue the motivation for not having, let me call them purely anonymized, the motivation for a notion of encryption was that as epidemiological information accrued over time to the sample that could be important to the research and that we wanted that to be able to pass through, okay.

So coming back to my example, from what I have heard I come to you, all right -- by the way we have done this. We have come to you, right, and said we want access to the Framingham samples. We get them in from our perspective, millennium's perspective, in anonymous fashion, right. We do not know who the heck we are -- they are.

But it would be really nice as we are doing our research if additional longitudinal information accrues to what for you is sample John Jones for me is sample

whatever, that information floats through and that was our primary initial motivation for that even though there is -- why not pure -- not purely anonymized but encrypted so the epidemiological information flows through.

DR. OLD: Right. So --

DR. HOLTZMAN: -- so in your terms if epidemiological information continued and can flow through to the sample --

DR. EMANUEL: Without identifiers.

DR. HOLTZMAN: -- without identifiers, is that anonymizable?

DR. OLD: No.

DR. HOLTZMAN: That is not.

MR. CAPRON: It is identifiable.

DR. OLD: That is not -- if -- and the researcher has to decide --

DR. HOLTZMAN: Okay.

DR. OLD: -- if for some reason you need to know something about those participants then that is identifiable.

DR. HOLTZMAN: Okay.

DR. OLD: And that is not anonymous.

DR. HOLTZMAN: Okay.

DR. OLD: And it is up to the researcher to

decide if you truly want something anonymous or anonymized you are not going to go back, you cannot go back, and if you want that possibility then it is not anonymized.

DR. EMANUEL: Wait a second. We are confusing things and I think we need to be clear. Because you are getting additional information does not necessarily mean you can walk backwards. The whole thing that the NSA is worried about, right, with encryption is that it can go one way and they cannot find out going backwards.

DR. OLD: Right.

DR. EMANUEL: Even though continuous information can flow they cannot go backwards. So just because you can get more information does not correlate with as I have heard repeatedly with being able to walk backwards. We need to be clear. Your way of encrypting three different number codes, you throw out the middle one, does mean you cannot ever go backwards.

DR. OLD: Which means that you cannot have further data flow.

DR. EMANUEL: Right. But there are other ways of having further data flow that still prevent you from walking backwards.

DR. OLD: Sure.

DR. EMANUEL: And we need to be clear about

that because these are not equivalent phrases and we keep tossing them around equivalently. In our proposal or suggestion or thinking about this the possibility of having continuous information updates, as long as it is stripped of identifiers, still makes the research to be done in an anonymous manner. If I understand you correctly that is not possible in your's even if you cannot walk backwards.

DR. MURRAY: That is correct.

DR. EMANUEL: And that is one of the reasons --

MR. CAPRON: It is the category.

DR. EMANUEL: What I would say is that is one of the reasons we threw out these categories.

DR. OLD: Right. I think what this group is saying is that if you want that possibility you should run it by an IRB.

DR. EMANUEL: We do not disagree with that.

DR. OLD: I mean, that -- and that is what our distinction is, is that it should be run by an IRB and, you know, if the IRB says, "Oh, we consider that anonymized even with further data flow," then that is what the IRB says but it should go through the board.

DR. EMANUEL: Okay.

DR. HOLTZMAN: But I think this is a very useful discussion because as we come back to the points

Alex had been making it is to focus on whether the sense of anonymous versus encrypted that is important from your perspective is that additional information flowing or the walk back possibility.

DR. MURRAY: We need to -- it is obvious to me that we need to be crystal clear in our report that we make these distinctions clear and why we choose whatever we choose in the report to adopt one particular way of construing it for policy purposes and that is really what in the end we are talking about.

This is being -- this is very helpful.

Zeke was on the list. I do not know -- is that what you wanted to say, Zeke?

DR. EMANUEL: All the questions were asked.

DR. MURRAY: Okay. We are coming up -- Carol?

DR. GREIDER: I just want to make one quick point again getting back to the issue that we were using the term "used in an anonymous fashion" and reiterate that I think that that is a useful term because I think that what we were just hearing we would define that as used in an anonymous manner. If you use the term "anonymized" that to me is more confusing because there are some people using the exact same tissue in one way and some other people using the exact same tissue in another way and I think that

that -- keeping that distinction is a good idea.

DR. MURRAY: Bernie wanted to say something.

DR. LO: Yes. I want to make a suggestion for the commission. Our discussion is predicated on an accurate understanding of what encryption is possible, what the risks are, you know, is it possible to have -- how feasible is the technology to allow us one way transfer without reidentification. I think we should ask an encryption computer person to come and talk with us to first teach us sort of what is the state-of-the-art and what is likely, and also just to ensure that we are not saying something that sounds good on paper but is just not feasible or inaccurate from a technical computer point of view.

DR. COX: Ten seconds?

DR. MURRAY: Yes.

DR. COX: This has been extremely helpful because it is this issue of flow through of additional information that is encrypted.

DR. MURRAY: Right.

DR. COX: And how much additional information can flow through and have it really be anonymous, that is when the researcher does not need a close personal relationship, okay, with the subjects. That is the name of

the game here.

DR. MURRAY: Well, there are actually two -- at least two different meetings. I think Zeke did a nice job but let me reemphasize them.

One is how much information is stripped from the sample as it is sent forward to the researcher? Given what we know about the set of samples that are out there, given publicly or otherwise available to researchers databases or sources of information, can the researcher get back and learn the identity of the individual? That is one important meaning and I think our -- that is key for us. Samples used in an anonymous manner in our -- my understanding of it at least would say that if, in fact, the researcher gets sent the tissue with whatever accompanying information cannot reasonably discover the identity of the individual, that for me would be in an anonymous manner.

A second issue is does anyone retain a kind of encryption key that would enable them to either send information further forward and/or be used to discover who the sample is linked to. That is a second question so it can be -- you can have research -- you can have samples used in an anonymous manner by the researcher with or without some existing key and there might be -- there would

be reasons for and against having such a key in different circumstances.

DR. COX: That is your formulation. That was not the formulation I was just making. The formulation I was just making was viewed in a different way, which is look at the amount of information that flows through. If at the end of the day that you are asking for all the information besides the person's name and social security number to be updated to you on a regular basis, okay, even though you are saying that it is anonymous I am questioning, okay, what that relationship is that you are really having with the individual patient.

DR. MURRAY: That is the first thing.

DR. EMANUEL: Well, let's just think through something like Framingham or the Nurse's Health Study. You get some physical exams on an every two year basis I think on the Nurse's Health Study. That information minus who it is then goes through a machine to encrypt it and is attached to a number. That does not require the researcher having any relationship. It does require an infrastructure of the researcher sending out the surveys, data inputting it, but the researcher who looks at the data at the other end, right, has no idea.

Now how difficult or whether it is literally

impossible, and again I think this goes from a -- it is not even -- I mean, impossible, I guess, means just many, many years with, you know, super computers out to -- you know, it is pretty difficult. It will take someone who really wants to know a few weeks to do it. How difficult that is, is the issue.

DR. COX: I get you, Zeke.

The next step, and that is fine, so it is just like prepackaged stuff you get.

DR. EMANUEL: Right.

DR. COX: But then you say, you know, I would actually like you to go back to the person and find out a little bit about this. I do not want to know who they are but I want you to ask them a specific question for me.

DR. EMANUEL: Well, but in my view, David, that changes the research completely.

DR. COX: Well, but that is still anonymous under the way that NBAC is talking about it right now and that is a really different issue for me.

MR. CAPRON: Tom, on a separate paragraph for Susan, to pursue Steve's line of questioning, on page 15 the paragraph beginning "No specimen" it seems to me that that is another basic difference in the use of already collected data from the approach that the subcommittee has

recommended so far here because as I read this unless the research -- the present research is broadly related to the goals of the original study, that is to say the original basis for collecting the tissue, it cannot be permitted even with anonymous data.

Is that a correct reading?

DR. MURRAY: Yes.

MR. CAPRON: It does not say go to the IRB. It just says, "No specimen."

DR. MURRAY: I think that is a correct reading.

DR. OLD: I --

MR. CAPRON: And that is a very, very sharp difference because although David Cox is a member of both groups, in this group as of now the subcommittee is not taking the view that Rhetaugh had raised before, which is every effort should be made to contact someone if you are using a specimen that they have not said you could use the way you are going to use it but has rather said the stuff is all there and as long as it is anonymous you do not need any IRB review, you do not need any consent, you do not need any community consultation, you can use it, and then a lot now turns on the last 15 minutes of conversation about what anonymous means but that -- and this says, "If you collected this to study pulmonary dysfunction and someone

is coming along and wants a bunch of samples to study liver disease you cannot give it to them for that reason."

DR. OLD: Not exactly. The way this --

MR. CAPRON: This policy is --

DR. OLD: -- policy is set up is that if you want to do that you need a whole new study. You need to go to your IRB. You cannot use an anonymous -- unless the -- you know, unless that is part of the IRB but you need to go to an IRB with a new proposal to study those stored samples to do studies that are not broadly related to the reason they consented to in the first --

DR. HOLTZMAN: But you do not have consent.

MR. CAPRON: Now you have confused me.

DR. HOLTZMAN: Yes.

DR. OLD: Well, you do need --

MR. CAPRON: This says, "No specimen can be used." It does not say except with IRB approval.

DR. HOLTZMAN: Alex? Alex?

MR. CAPRON: So I am trying to -- I am not trying to argue with you but in -- what is that? Should we read that an IRB may give permission for an unrelated study to be done?

DR. HOLTZMAN: The focus on the parentheses in the first conjunct, in the first disjunct, right, you have

got an unless a new consent can be obtained in the first disjunct but you do not have it in the second.

MR. CAPRON: Where?

DR. HOLTZMAN: Okay.

DR. OLD: And that may be due to several rewritings of this paragraph but I think --

DR. HOLTZMAN: So did you --

DR. OLD: I think that what -- I think the intent is that as it states earlier in here that if it is not broadly related to the original consent you cannot use it for future studies without doing extra efforts.

MR. CAPRON: But the extra effort would be getting a new consent.

DR. OLD: Getting a new consent, going to an IRB with a new proposal, yes.

DR. DUMAS: It does not say --

DR. OLD: It does not say that. You are right. You are right.

DR. DUMAS: It says get a new consent.

MR. CAPRON: It says if they say you could not use it and you now want to use it you have got to get consent. If they said you could use it for a study of pulmonary disease and you now want to do an unrelated study you cannot use it. Are you saying that is not what it

says? What it says is you cannot use it unless the IRB says you can use it?

DR. OLD: I think -- yes, I think we are getting into some semantics here. I think that you cannot use it anonymized --

MR. CAPRON: I do not think this is semantics.

(Simultaneous discussion.)

DR. OLD: You cannot -- it is not covered under using it anonymized. It is not covered under this part that says that sharing can be done if it is anonymized. If it is not related to the original informed consent you cannot use it anonymized. You need to do these other things that it talks about.

MR. CAPRON: What other things does it talk about?

DR. OLD: Go to the IRB.

DR. MURRAY: I think I detect a level of fatigue setting in and we really do need to take a break. I want to thank Dr. Susan Old very much for coming.

DR. OLD: Thank you very much.

DR. MURRAY: Can you stay for a while, Dr. Old?

DR. OLD: Sure.

DR. MURRAY: Thank you.

We will reconvene in -- I have about 21 after.

We will reconvene -- try to reconvene at 10:30.

(Whereupon, at 10:22 a.m. a brief break was taken.)

DR. MURRAY: I want to thank Patricia Barr for joining us this morning.

Patricia, I have heard a great deal about you.

Can we provide a microphone for Patricia Barr to use? We have got one.

CONSUMER PERSPECTIVES ON CURRENT ISSUES

(Slide.)

MS. BARR: It is easy for me to speak strongly about this topic because I have been working on it for a long time.

I am an attorney. I come from Vermont. I am the chair of the Ethics Subcommittee of the National Action Plan on Biological Resources and I have been for the last six years a very active member on the National Breast Cancer Coalition. The Coalition in '93 had a campaign in which we called for a national partnership, public and private, to look at key issues in breast cancer and it was out of that petition campaign, which collected 2.6 million signatures that we developed the National Action Plan in Breast Cancer, and then I was lucky enough to be appointed to do some work with that group.

(Slide.)

Now we dealt with clinical samples, samples taken in clinical practice, and we dealt with some of the practical issues. So the approach that I am going to be presenting compliments to some extent the approach that you just heard earlier.

Let me talk about what we decided to do because of the quagmire that we found ourselves in when we took on this issue. One, we limited ourselves to prospective collection because retrospective collection we felt as a starting point was going to be a very difficult starting point.

We were most concerned with samples taken in routine clinical practice because many samples that are available for research are those samples held by individual pathologists who may or may not be affiliated with a research institution and we -- this program motivated by patients and advocates -- were very interested in ensuring that the role of the tissue donor was seen as an active role and a role of a partner. We wanted to develop user friendly -- a user friendly consent process, not just a document, that was going to be meaningful to both patients and researchers and we were looking to standardization because we believe standardization will facilitate research

and our goal was to facilitate research.

(Slide.)

I want to talk about what we produced because you have -- and you have it. It was distributed in your meeting materials.

We produced a consent form and it was initially a layered consent form. We produced an informational brochure because we felt that the form itself would not -- was not explanatory enough and we knew in clinical practice things were going to have to be somewhat telescoped in.

We have a model for "banking" operations that I think addresses some of the concerns that I have heard raised before this morning and we provided principles for use in tissue collection and dissemination. We take a very strong position that we would like to distinguish between IRB's. There are IRB's that review research protocols. The researcher wants tissue and his or her institutional IRB is going to review that protocol.

We believe there should be an IRB affiliated with every tissue resource. So if a pathologist, indeed, has collected samples and that pathologist is willing to distribute those samples that pathologist is a tissue resource and, therefore, certain principles should be in place for the operation of the distribution of the resource

and there should be an IRB that is ensuring that those particular principles are followed.

Now I should say at this point that it was always understood that though we were funded by the National Action Plan on Breast Cancer our work was to be a model and, therefore, we do not see this work at this point as only pertaining to breast cancer samples but see it as a model for any tissue banking that is done and tissue resource distribution, and that the language in the form is easily modified and, in fact, the PRIMER working group that took us on from us has done a lot of that modification.

(Slide.)

What are the challenges even to perspective collection that must be addressed? The independence and variability of expertise found in IRB's. The limited resources of IRB's. The IRB community responded to what we had presented saying how can this be paid for, how are we going to do it, and the informatics and processing difficulties in giving donor's choice.

When you are not in the research setting, when you are in the clinical setting and an individual donor is given the choice of this can be used for cancer research only, this can be used for all research, this can be used for all research except behavioral research, I only want

this used in this way or that way, you get a very difficult storage problem. You get a very difficult coding problem. You get a very difficult transfer problem.

So as much as we wanted in the clinical setting to layer the consent form and as much as we wanted to give choice to the participant donor we opted because of the practicalities for two choices, "I will participate and my tissue may be used for cancer research, my tissue may be used for other research." And even with that the pathology community is very concerned.

NCI is working with them now on costs and management of the process.

So there are costs to pathologists that is real time and money in clinical practice. There are costs to the surgeons in real time and money in adding anything to the standard consents that they now use which we deemed totally inadequate for the purpose.

And then we have come to learn that in clinical practice pathologists will routinely throw samples away. If what we are truly concerned with is the value of archived tissue as a national resource then, in fact, we have a problem about not only keeping the codes right but keeping the tissue properly stored for use.

(Slide.)

We are working on solutions or we have handed this over to other people to work on solutions. We wanted to summarize and stop doing this. Let me say by way of background that before I began doing this work I certainly was an advocate, I am an attorney, I did not particularly do ethics work, and I came to this with a kind of naivete and impatience because of my status that have proven to be very useful because people who are naive and people who are impatient tell other people, "Well, we can get this done," and they keep pushing and it gets done, and the group that worked on this was very multifaceted.

There were pathologists. There were ethicists. There were other consumers. There were population studies people, public health people. There were surgeons. So there was a wide variety of mix. There were academicians and there were clinical practitioners in this group that worked on all these.

So where are we? We handed our model documents to PRIMER or PRIMAR and they have put them together very beautifully with a summary of the joint meeting we had with their concerns and have distributed them at their plenary session at an annual meeting just last month with feedback information.

Now some of that concerns me. When we took

this material and we were looking at OPRR and said, "You know, we need to move to guidelines for IRB's because if we let them all flounder with their various levels of expertise we are not going to facilitate research and every researcher who wants to use tissue is going to be up against five different standards if he is going to five sites for a multisite program, ten different standards if it is ten sites for a multisite program.

So there needs to be some standardization and what we were told is, "Well, NBAC will do this." So I feel greatly honored to be here before NBAC in great hopes that, in fact, you will do some of this and that will provide guidance to the IRB's who are concerned about their ongoing role in this area.

One of the things that we -- that was most controversial and what we suggested that I think is very important is that there should be a panel associated with every tissue banking enterprise that will review protocols that come into it so the protocol may be reviewed by the researcher's institution that wants to support a researcher doing certain work but tissue is a limited resource. It is becoming very limited in breast cancer because of the size of tumor when the tissue is taken but I am sure that this is an issue in many other areas.

If you have a limited resource then you have to prioritize how it is used and there has to be conversation with communities of interest about how it is going to be used. The concept we were talking about earlier which is community collaboration or community consultation. Someone has got to do that and there have to be standards for how it will be done.

It seems the likely place for that to happen is with the tissue because they get an overview of what is being requested, the timeliness of it and the amount of it. So we have suggested that an IRB affiliated with a tissue banking institution have -- appoint a panel that will do that kind of review.

IRB's do not want to be responsible for that panel. When we asked them, "Well, if not you, who?" There was no answer.

So I will say to you, "If not them, who?"

But clearly that is a very important function in all this. It is a vital function in all this.

What needs to be done? Just clear OPRR or NBAC guidelines. Just what I have talked about. Some standardization of documents so researchers do not get approval in one place, then go to the next place and have to change it and then go back to the first place because

they need consistency in their trial. If they know they are using tissue and we can simplify what has to be done so that they can use the tissue we will have facilitated research. That was our goal.

And finally because we are looking at testing in a clinical setting we are doing some pilot testing with NCI of using this consent in the clinical setting. And what we have done with is it is an add on to the general surgical consent and we are doing some pilot testing and presenting it at different times, sometimes in the doctor's office and sometimes unfortunately the night before because that is when it really happens, and trying to get feedback.

You should also know that we focused group the documents and as a result of that working with different ethnic communities we got a lot of very good feedback on how to change the documents and it was from that process that we did the informational brochure.

(Slide.)

A few more solutions. NCI is actually working with professional groups now regarding costs and storage guidelines. That is going to be a long process. NCI and DOD are talking about a national storage system. That is very preliminary. And then we are in a world where there is ongoing attention to informatics, questions of encoding

and safety.

Now what we did about the flow of information is that we said tissue needs to be used and no one can know today what the uses will be in five years or ten but that we can predict today that the valuable tissue will be linked and it will be linked to clinical information and that the need of the researcher will be for the clinical information with the tissue. And, therefore, we needed to come up with a model that could satisfy protecting the individual but allow the research to proceed.

The model that we came up with was a fiduciary standing at the tissue standing with the bank. They devise a system for collecting the tissue and they send the tissue out with the appropriate clinical information but without the identifiers. Coded information is what we have used that we think is essential.

Now I believe we can apply some of this to the archive samples that exist but we for political reasons, very good political reasons, look forward rather than back but I know you care about back so I decided to be brave and talk a little bit about backwards.

(Slide.)

The existing resources are vital. It will take us a very long time to get consents today and then

prospectively deal with the longitudinal data that we want. The consents that are in those surgical practices are totally adequate so there is no way we are going to fix that. And it is not practical to reconsent. The cost is just too great to reconsent in a clinical setting. Research setting is different. In clinical setting it is not possible. So either we throw that stuff out, which I think would be a tragedy, or we come up with something that is going to help and make it possible to use it.

When I first got into this field what was interesting to me was there was a profound conflict about ownership of the tissue. Pathologists thought they owned the tissue. Patients thought they owned the tissue. Now what I have learned to do, and I used to do a lot of mediation, is decide that the best thing to do is not talk about ownership. So I put it up here as a problem but it is a problem we can skip. We can jump around. We can dance around. What we talk about now is fiduciary responsibilities which is pretty comfortable for everyone to talk about and the pathologists agree they have a fiduciary responsibility here.

If we are going to proceed to use archived samples we must have public confidence and if we do not have it we are going to lose our ability to do prospective

research as well and that public confidence must be earned. It is not going to happen. It must be earned.

(Slide.)

So what are the considerations? We are going to have to establish standards for population studies using archival tissue. We are going to have to protect individuals the best way we can and we are going to have to address the interests of communities when we do population studies. We must provide adequate compensation for those who manage the collections and we have to standardize the management of the collections. I think those things are just essential.

(Slide.)

I want to talk a little bit about the pathologists because I know they talk a lot so I will talk a little bit about them. They have a fiduciary responsibility with respect to the patient. They acknowledge it and they talk a lot about it, and that is to ensure that what is there is preserved for care, patient care. They have a fiduciary responsibility also to the resource itself and this is where we are breaking new ground where we begin to think of these resources not as belonging to the pathologist but belonging to the research enterprise and that the pathologist is the fiduciary of

that research enterprise.

They become -- in a national system they are not the arbiter of who gets to use the tissue they hold. Now today they are the arbiters of who gets to use the tissue they hold. So I am presenting a radically different approach. But they do deserve adequate compensation for the work they do in serving as fiduciary responsibility to the research enterprise as a whole. I think that the model that we put in place of a neutral third party, the IRB and the tissue bank, is applicable to archival collections as well as perspective collections but the standards for what must be done in a population study or other study when we are using archival tissue is obviously going to be somewhat different than what it might be in a perspective situation.

(Slide.)

I am going to talk just briefly about standardization and then I think I am done, almost done anyway.

Standardization impacts donor participation and I came to this enterprise because people wanted to help the research process. Now that is a limited population. There are populations that are much more skeptical than the population I came from and there are portions of the population that I speak for that are more skeptical than

other parts of that population. But there is an interest in doing good and there is an interest in doing good particularly when you are faced with fearful circumstances. It is a way of gaining control and experiencing some sense of control.

I would not underestimate that as a benefit to those who donate tissue for research but we have got to make it simple for those people because as you have talked about they are under a tremendous amount of stress. It has to be a system that is easy enough to explain and there is some discussion of it in the world out there. It is not a secret of researchers and academic institutions. You have to give these donors access to this system so it should not be dependent on, "Well, I have a doctor who is willing." There is some presumption that there is a way to access that system.

Lack of standardization hampers research. It makes locating research is very difficult for researchers and the hoops they have to jump through because every site or every IRB is quirky are unreasonable. They are just unreasonable and time is lost and we cannot do the kind of multisite studies we want to do.

(Slide.)

So how do we deal with anonymity? I think that

you have been struggling with it. I suggest that we separate the researcher from the linkage using a third party trustee. We insist on community participation and resource use review and we strictly limit reporting of individual results.

My subcommittee said we just do not do it. Done. Easy. No.

The IRB said don't be so limited. There may be a very important situation like a misdiagnosis that is discovered where you want to be able to get back to the patient. So we have strictly very rare -- and we put in some adjectives removed -- removed from that. But those are some of those factors that have to go into continued use.

(Slide.)

And the practical realities are we have got to come up with something relatively simple if we are going to do in clinical practice. We have to frame the solutions for the real reality out there. There is a lot of tissue out there without adequate consent. Every problem can be solved and many of the economic solutions and the solutions will be found in partnership. I think that is true of the Action Plan's experience that there has been a lot of betting, there has been a lot of concern, but in the end we

moved forward in a very constructive way and we have been able to gain a lot of support for our work.

DR. MURRAY: Thank you.

Time for questions.

Alex, Bernie and Zeke?

Try to hold this microphone very close and be heard.

MR. CAPRON: I will try.

The presentation I have found was very informative and I want to thank you for the obvious work that has gone into it. I hope your expectations that NBAC will solve everything for you are not exaggerated.

There are times when I wish that a couple of the major figures in the history of human experimentation and the analysis of it were with us. One of them, Jay Katz, could be; another, Hans Jonas, cannot.

But the three thoughts I want to introduce along the lines of what Rhetaugh was doing in saying let's stay with fundamentals are the framework for a lot of what goes on in the field thinking practically is one in which researchers, physician researchers, begin from a sense of basic beneficence that they want to do good and that that sense of wanting to do good has at least in the past, not to speak to any present or future physician researchers,

has led to a lot of paternalism. I am sure that in the breast cancer community that has been an issue to which a great deal of thought and writing has occurred but it is something to keep in mind here and it came through in your comments also about the pathologists. The sense that I have a resource, I want to do good, I want to determine what happens with it.

The second is a phrase that you used about the tragedy of not doing research and it is here that I want to invoke Jonas' ghost because I still am convinced by his view that the greatest tragedy is doing things which end up harming or wronging people in the name of the greater good of progress and that progress in his phrase is an optional good and it is a good which ought not to be bought at certain other costs which can occur even in well intentioned circumstances. Now obviously he was not -- his was not an argument for doing nothing but it is a question of what presumption we go into things with and in that line I would like to put four points to you and ask you to elaborate on them because they were so intriguing as you went along.

The first one was the notion that with some of this research, particularly I guess on retrospective research but maybe it went to both, public confidence was

essential and you said public confidence had to be earned. I want to know have you given in your reports you think some attention to how it would be earned? Would it be a matter of a researcher being very public that I am going to be going to X, Y, Z source to get the tissues there and the research I am going to be doing is this and here is the protections that I have erected, and because I am not going to the individual women from whom the samples came I am going to the community. So, I mean, there is a public notice, as it were. If this bothers anyone who thinks that her tissues are there let me hear from her. Or is it a matter not of that kind of confidence that you actually would be able to have some say at a later time but something else?

The second question is to ask you to tell us why this phrase "fiduciary responsibilities" was used. I understood one way in which it was being used. If I am a pathologist and I hold tissue I have a responsibility that the tissue continue to be usable for the clinical benefit of the women from whom it came. So that means I should not expend it all or I should not lose it or mislabel it and so forth.

But part of the other notion of fiduciary is usually a fiduciary should not use the property or other

things that are those of the beneficiary, the ward, or whoever, the client, in a way which benefits the fiduciary and does not benefit the ward.

I mean, that is sort of -- and yet it does seem to me as though what you are talking about here are situations in which that on the surface would be -- I mean, if you see the person holding the goods as in some way related to the research project and as furthering research if it is done without the consent -- I just want you to say why that term really applies because fiduciary is a very -- to me is a very high standard and it invokes a lot of connotations which are different than paternalism and beneficence. There are some fairly strict ideas.

You may have other ideas and, if so, I would favor another term.

The third point is you talked about the burdens of allowing patients to define their role as subject and you explain that that led you just to make the two divisions that you made. We heard from the presentation that Susan made that many more divisions and a more refined consent process were being thought about.

What it seemed to me you were saying was it would simply cost too much.

Now research would also be easy to do if we

could commandeer laboratory space, and pipettes, and beakers, and solutions, and so forth but we do not. We regard those as things on which money has to be spent. I want to understand if what we are talking about here is simply a trade off. It would be more expensive.

Are you saying it would be logistically impossible to have a code attached to each sample because we are only talking here prospectively obviously, a code attached to each sample and so if someone says I want to have the available breast cancer -- the samples that meet the following definitions that you would run the computer and it would say, "Well, these women said you can study it only for breast cancer and you are doing another study so they are out and then these people said, 'I wanted to be recontacted before you did a study,' so we will have to contact them and if we are not willing to do that they are out, and so forth."

Is it logistically impossible or is it simply a matter that that would be an expense where someone would have to pay the pathologist or the tissue bank or whatever to do?

The third one is this thing that you came to toward the end which was a reason for breaking the barrier and you have cited one which would be an example of

clinical benefit. My God, that was a misdiagnosis and we ought to tell the person now that our lab has run a different study that they were misdiagnosed and that something went wrong. You suggested that you had worked out a statement of when the barrier could be breached back. You did not work it out. I thought you said you had some criteria.

DR. BARR: We compromised with the IRB's who felt that -- we compromised with the IRB community in working on these documents in saying that there needed to be room for IRB's to make decisions about when there could be a breach.

MR. CAPRON: Okay.

MS. BARR: Our committee felt very strongly that that would -- that was not appropriate, that you just do not go back because it is research, it is not clinical practice.

MR. CAPRON: I mean I have a sense that your earlier intuition, which is IRB's need a lot of very firm guidance on this, is right and whenever we say, "Gee, there is too much disagreement, we cannot figure it out, we are going to leave it to the IRB --"

MS. BARR: You are in trouble.

MR. CAPRON: -- that we are in trouble and the

variation you are going to get among IRB's from those that really have thought about this very well and really go through a very careful process to those for whom the issues just do not emerge and so they easily approve it or disapprove it is going to be extreme. I am very worried and I hope that -- this is to my fellow commissioners -- I hope that we in looking at it will think about what kinds of guidance that would be because that breaching the barrier and going back for "what are good reasons" is an essential issue on this anonymizable or identifiable, or whatever the phrase that we end up using, encrypted information.

But I have those other three points if you could -- I think you took notes on them.

MS. BARR: I did. Let me try and go backwards. On paying for the code, I basically come from a world that says you usually do not get the whole pie and that is because I come from a very political world. That was my prior activist sort of training. And so what I have learned is that you set -- sometimes move in incremental steps. And faced with a very large problem and a desire to move the process forward what our group did was locate two areas of grave concern in terms of facilitating research with research.

One was lack of standardization and guidance for IRB's and the other was the consent process. And so we did the work we did to address those problems. In doing that work we wanted to give the donor as much freedom to code as possible but it seemed that at the state of technology and the world we were entering where they did not even give consent it would be a very good step forward to insist on consent and then at least offer choice. As a community gets used to simple choices then perhaps we can add more complex choices as our informatics become more sophisticated.

In an ideal world would I be standing arguing for really sophisticated coding? Absolutely. But in a world in which there was going to be significant resistance from clinicians who are not researchers and who had a resource that researchers were going to want to use we made a judgment.

Now if this group believes that the research community itself can get enough tissue for research purposes specifically designated for research purposes without going to the clinicians in the world, that is an interesting point. It does mean that participants like me, who may have her biopsy in a local hospital, never get to participate in the enterprise. So am I willing to trade

off a lot of choices for some participation? My view is yes. Others might not and they can say no.

MR. CAPRON: And how do they say no?

MS. BARR: They say no by not agreeing to research or not agreeing to other research in the consent but at least that gets out to the public, which has a number of benefits. It allows individuals to participate. It raises our confidence in the research enterprise because a lot of people are participating and there is some exposure.

Now the issue of fiduciary --

MR. CAPRON: May I ask you --

DR. MURRAY: Alex, I am going to have to --

MR. CAPRON: Well, let me --

DR. MURRAY: In the interest of time, we have about 30 minutes left for all of this morning's conversation, unless it is really urgent I am going to ask just to let Pat finish.

MS. BARR: Okay. On the issue of fiduciary you have identified the traditional notion of what a fiduciary is and I am perfectly willing to change the word but it seems to me that what we are talking about here is that the pathologist has to stand apart from his or her world as researcher and that they have no higher right to use the

tissue that they hold than anybody else.

DR. MURRAY: Thank you.

MR. CAPRON: And public confidence?

MS. BARR: And the public confidence issue is exposure -- public exposure of this kind of debate. IRB's, local IRB's having a duty to inform their communities of what they do in some way through local hospital newsletters or whatever, guidelines for that sort of thing. Ensuring that communities of interest have a role in design of research and advisors to research panels, and advisors to consortiums. That would be a -- those three things would move us forward again incrementally but significantly.

DR. MURRAY: I have noted Bernie, Zeke, Carol and David expressing an interest to say something. If anybody else does or I have missed them please let me know.

Bernie?

DR. LO: I want to thank you for your presentation and also the material you gave us.

I have several questions all in the theme of trying to understand better the point of view of patients living with conditions for which these research might be done.

First, you said -- I think your message came through very clearly about the urgent need to do research

and how having the option to participate in research gives a sense of control and be beneficial. Could you also talk a little bit about what are the concerns that women with breast cancer have about these sorts of archival projects?

The second question has to do with the consent process. To amplify some themes that Alex raised, are there barriers to a layered consent process from the point of view of the woman at different stages of breast cancer so that we had heard some anecdotal information that, you know, you have so much on your mind at the time of diagnosis, definitive treatment, that really is not the optimal time from the woman's point of view to enter into the kind of nuance layered discussion that Dr. Old was talking about. So again most of the barriers you were talking about were barriers from the clinician side or from the cost side. Are there also barriers to a layered approach to consent from a woman's point of view?

Finally, if you could --

MS. BARR: Okay.

DR. LO: We all try and get three questions under the guise of one.

So part 2B or part 3 is could you address the issue of being recontacted?

MS. BARR: Yes.

DR. LO: You said that your group was very much against having recontact to provide research information back to women and yet other advocacy groups have said, "Give us the information and let us decide, do not tell us it is still experimental, it is our body, let us decide."

Apparently you wanted an exception when there was clinical information that would make a difference to the woman, like a misdiagnosis, in either direction, more serious or less serious. How about being recontacted to be invited to participate in a research study in which it would be an identifiable link study? Is there -- is that a benefit? Is it a harm? It obviously is going to be different for different women but what should the policy be?

MS. BARR: Let me tell you about the policy and the evolving policy. The policy of the Action Plan Working Group was that recontact for additional research was enough of an invasion that an individual should, indeed, agree to it at the time they donate tissue. I am going in for clinical work and one of the decisions I have to make is do I want to be part of this ongoing or not.

The IRB community said that to promise that you would not be recontacted unless you gave your permission, which is what it is to ask that question, is misleading

because there is information in registries. There is information in other documents. So researchers might contact you anyway for information and, therefore, a particular tissue banking enterprise to make the assumed promise that you would not be contacted. Although they could promise they would not contact you, it would be confusing and irritating.

So we have another practical dilemma.

My personal view is that, particularly if you are dealing with genetics, recontact about a study of genetics when you did not know your tissue was being used in a genetic study is an incredible invasion. I do not know how we put in place the appropriate protection. What I am telling you is my view, not a study view, and I think one of the things that is clear is that the whole area of study of what a response is and what is important is a study that is something that has to evolve and we need to be putting more resources into that.

I do not think any representative patient group can really talk about what their constituency wants because you are generally listening to the most educated, the most -- you know, the strongest advocate speak and so we need other ways to do community consultation to get other points of view.

What are the concerns of those active? They are about discrimination. They are about being given information you did not want. The right to not know as well as the right to know. And we are very concerned that the community understand the difference between research and clinical practice and that there be an understanding that significant amounts of research must occur before things get to clinical practice.

Now that is not a desperate position. There are people who are suffering from disease who feel a great deal of desperation and I am sure that if they were sitting in this room or if I were in their shoes I would have a different view about where the line is between information I should have access to versus not. So I do not want to pretend that my view is more appropriate. I just want to explain where it comes from.

DR. LO: Could you just comment on barriers to a layered consent process from a woman's point of view?

MS. BARR: I think if we have a consent process that is not the night before and if we have a consent process that will occur in the doctor's office either with a trained nurse or someone that the patient at this point is trusting, and I think trust is what is important, then I think patients will be able to handle layered informed

consents. I do not think it is a complex -- I do not think it is any more complex than we would like to use your tissue for research to say are there certain things that matter to you about how we use your tissue.

I think that the compromise here was a practical one from the medical community's point of view and again it was our belief that we wanted to give patients an opportunity to participate. They do not have it now in a knowing way. So this was step one to give them a way of knowingly participating.

DR. MURRAY: Thanks, Pat.

Zeke?

DR. EMANUEL: Like my fellow commissioners I want to thank you for an excellent and spirited discussion.

I would like to identify -- I found many areas in which your approach is very consonant with the subcommittee's approach. I think overall there is very little disagreement and actually a lot of agreement, including the issue of standardization of rules for IRB's trying to create a framework that is uniform to minimize exceptions so that people know what the rules are while recognizing that in some cases there may be extraordinary reason.

This issue of ownership is one you did not hear

all morning because we also, I thought, agreed that ownership was a bad way of looking at it and at least in our mini-hearings found that most people did not have a sense of ownership. That is not to say no one does but to say by and large it is actually not the view that seems to be dominant.

There has been spirited discussion and some disagreement about not going back. Some of us believing not going back is the right policy. Others worrying about occasional exceptions.

The one thing I would like to raise, and I think this follows up on Bernie's comments, is it is not just a problem of informatics here, this layered consent. One of the advantages, I think, the Breast Cancer Coalition had, the same way that Heart, Lung and Blood Institute had, is they are dealing with specific diseases going in.

The problem of writing a general consent not for a specific disease is much more difficult I will submit to you having tried it and I have encouraged all my fellow commissioners to try it because it is not so easy if you are going to take out -- if I go in for a breast biopsy, first of all what happens if it comes out benign is the disease that is similar cancer or is it benign breast diseases. You are already making certain assumptions.

MS. BARR: We made the assumption it was cancer generally. That was what our language was.

DR. EMANUEL: But if I turn out to have a negative biopsy, you know, what I have consented to then if you say can be used for similar diseases. Is it cancer or not or is it just benign breast diseases?

You have already made certain assumptions that someone who goes in for a breast biopsy you are going to put them in the cancer classification even though if it is negative for them they might have gone far away from the cancer classification and they are now normal. Similarly for many other conditions.

I think again the issue is not purely an informatics and money issue. The issue also is we may feel in our ideal notions of what informed consent does that the more we delineate the bigger that piece of paper is the better the consent.

My suggestion is the more layers you have we, as ethicists, may feel more comfortable but, in fact, the process may be inhibited. What we need to concentrate on is not have we given 12 boxes as opposed to two boxes but do the people out there have a reasonable sense even if we have not included all the specifics and that is why I -- my own view is not because of the informatics necessarily and

the complication and cost of the pathologist but for the comprehension and the consistency of the people out there and making sure that once it is implemented without draining all 600,000 doctors and X million nurses, we can be reasonably assured that people are going to know what is out there.

So my -- I first was against your form, then very for your form, then having tried to do a general form coming to the view that a layered consent is a good idea but probably two layers is the limit you are going to get.

MS. BARR: Yes. You know, I think that I probably agree with you about all of that and I think also that we struggled in an earlier edition of a genetics question specifically.

DR. EMANUEL: Right.

MS. BARR: And took it out. It is not clear to me that if you are going to work on a general consent and you might want to break down into genetic -- germ line genetic research versus other research as the right -- as a way of breaking this down with the two choices and that we might want to beef up the informational brochure about just what that is and what its implications are. We talk about it in a pretty simple way in our informed consent and in the brochure and that was as a result of focus groups which

in this -- for this particular exercise were very useful.

DR. MURRAY: Thanks.

Carol and then David?

DR. GREIDER: I just wanted to reiterate what Zeke said and I felt listening to your presentation that in the broad brush strokes that where you were coming from was very similar -- like I said -- in the broad areas of where the subcommittee at least was going. Some of the details may be different but I think that in general we are on the same page.

One thing that you pointed out was different is that you were suggesting an IRB for tissue resource and the question then becomes what is a tissue resource. Ms. Elisa Eisman put together for us a very nice summary of all of the different kinds of tissues that are collected and it is not clear that you can define -- some you can define -- as a tissue resource and it is there to be a tissue resource and some of the NCI resources but others are just a researcher that decides that they want to get together with a surgeon and do a study.

So how can you have an IRB when you do not necessarily have a defined group?

MS. BARR: I think that by carefully delineating the principles and I think our's are pretty

good but that is not to say they should not be changed or refined in some way, and then by saying anyone who collects and then distributes for purposes of research has to abide by those principles. So if I am a local hospital and I have got a doc in my local hospital who is doing this then my IRB in that local hospital has to take on that additional role of being sure it is done the best way to do it. Now it is not cost efficient, I mean, what we are again dealing with.

But where do we want to put our money in making sure this works? I think we want to put it in the fiduciary role of those who oversee distribution of tissue and I think we want to put it in that panel that reviews uses of tissue. That is where I think we are better -- we are better protecting people rather than trying to reconsent everybody who is in those archived collections of individual pathologists. It is a judgment call and maybe it is worth it.

I think the way I am suggesting allows us to continue to use those archived tissues where reconsent probably will not. So it is a compromise position.

DR. MURRAY: Thanks.

David?

DR. COX: Very rapidly, I really think that

where your statements are in process very different from what NBAC is doing, and I applaud your process, is to first have a goal that you are striving towards and that goal is not just how you deal with tissue samples but it is how you do research with tissue samples. I would just like to note that because I think that is the problem you are dealing with. Not tissue samples in isolation.

Secondly, is that by having a set of principles that you want to have guide what that product is going to be it helps then for you to define a process and that process of putting things in place for the whole endeavor is what you have done which is what NBAC has not done yet.

So I really applaud this as a process. I think that it would be a really good foundation for us to not only pay attention to what the scope of the problem you are looking at but the process that you use and the kinds of things that we would like to come out with. So it was really extremely helpful.

DR. MURRAY: Jim Childress would like to ask something.

DR. SHAPIRO: Got to be a rock star, Jim.

DR. CHILDRESS: The comment I am going to make actually connects with Zeke's discussion earlier this morning and the presentation. I think it is true that it

is -- well, I think it is useful to get away from the language of ownership as long as we do not forget that quite often in the legal context ownership simply refers to a bundle of rights and the real question here we are raising is who has what rights over what.

The reason for raising the point this way now is to now move to a consideration of whether we think in relation to Zeke's discussion presumed consent with the possibility of opting out really is something that captures all that we want. The reason I raise it -- if we think in the context of organ and tissue transplantation generally there is a lot of dispute about whether presumed donation, for example of corneas in states with certain medical examiner's laws, whether that really is justifiable presumption if people are not aware that their corneas can be taken.

So this is actually now picking up the ownership point moving to Zeke. I would like to know a lot more about what we can expect people to understand so that we can interpret their silence or their failure to consent is actually consent because that seems to me to be critical for how the recommendations work out.

DR. EMANUEL: Let me, I think, clarify. I think it is a good question. First, presumed consent with

opt out was something that had been suggested to us by Bartha Knopfers and I believe, and I do not want to -- if I mangled her name -- I believe I do not want to speak for the full subcommittee but we actually stepped back from that at our last meeting to a general consent. Okay.

I know it is on that --

DR. CHILDRESS: At least it still appears on the materials handed out today on --

DR. EMANUEL: That is because what I have included for you is a comprehensive -- not comprehensive, but a thorough list of a kind of history rather than the absolute latest. And let me -- in part because it is in flux. You know, let's just be frank about it. This is in flux. The recommendations are not written in stone and different people have different views of where they want to be. But if you look at the second to last page.

DR. CHILDRESS: And that is the one where you said there was an error that needed to be corrected, is that right? Because I still have presumed with opt out.

DR. EMANUEL: What I have here is alternative proposed policy. This sheet. The back of it says "key distinctions."

DR. CHILDRESS: Okay.

DR. EMANUEL: Second to last page.

DR. CHILDRESS: Sorry, I was not up --

DR. EMANUEL: No, no, this is confusing. Part of the reason is I was trying to get -- or had e-mailed to Henrietta a lot of the permutations that we had gone through and debated and discussed so people have a better sense.

So if you look here at what we have -- and I may not be completely accurate -- migrated to is a general consent and not presumed consent with an opt out.

If you would like me to defend the idea of a presumed consent with an opt out I would offer you --

DR. CHILDRESS: No, I was not interested in defending it but rather challenging it.

DR. EMANUEL: Right. No, I actually think it is a reasonable position but --

DR. MURRAY: But we are not adopting it.

DR. EMANUEL: But I am a minority and am willing to give in.

DR. CHILDRESS: That takes care of it. I am sorry. I was on the wrong iteration of this.

DR. MURRAY: Harold?

DR. SHAPIRO: I have what I think is a very small question, small aspect of what you are doing, but you have focused on clinical samples as I understand it in your

work. Do I understand your group to be saying that if a pathologist and a clinician, a surgeon of some type, decides to collect a sample for use in some way they want that neither of them has any privileged status in the use of that material but even if they want to use it for their own project that they have to go through the same thing the third party would have to go through or have I misunderstood that rather small part of this issue?

MS. BARR: I think you misunderstood.

DR. SHAPIRO: Okay.

MS. BARR: If I, as a surgeon, go to a pathologist and say, "I have a protocol to do this particular research and it is within an institution and we have gone through the IRB and they have approved it and we are going to consent every individual before we do the research specifically to that research."

DR. SHAPIRO: Then they are fine.

MS. BARR: They are fine. But if I, as a pathologist, have a collection of the last 15 years of patients who had been through my hospital and I am dishing this out, no, you cannot do that anymore.

DR. SHAPIRO: Yes. Thank you.

DR. MURRAY: I actually have myself on the list mainly to praise you and the work of your group, Pat. I

want to pick up on Jim's first point about how to understand property. Indeed, as I understand it historically, it is a bundle of both rights and duties. I think your group has stressed the duty aspect.

Courtney Campbell, who wrote a background paper for us about some religious views about the human body and how they might be interpreted for the kind of problem that is facing us came up with, I thought, a very nice variant of the whole notion of the human body as gift and he talks about in this kind of context it is like a contribution that you make. It is not a gift to a specified individual but it is a contribution to a larger kind of effort and socially desirable goal worthy of our support.

I think that is probably a good way to think about it in which the case the people who are then holders of that contribution have duties, not merely rights but duties, to handle it in certain respectful ways in keeping with the intent of the donor and the like. That to me -- and I have to confess that makes a great deal of sense to me. So that is the first item of praise.

The second thing I would like to do is Rhetaugh asked a question earlier, which I think really -- it is an important one. It deserves as full an answer as we can give it and we do not have a lot of time left before we

must begin to close the morning session but if I may try to repose the question.

Why don't we go back and why don't we simply have a rule that says for samples collected prior to our report that none of them may be used without explicit consent? I think that -- Rhetaugh?

DR. DUMAS: After hearing the presentation I --

DR. MURRAY: You need to use the mike.

DR. SHAPIRO: You have got to get close to the mike.

DR. DUMAS: After hearing this presentation I have had some second thoughts about that. I think, first of all, I would continue to feel that our overriding principles should be informed consent. If you have got a number of samples that you have had for a number of years and it is literally impossible to gain that consent then my next question would be what is the next best principle to use and I like the idea of the IRB's and the definition of the role of the pathologist. That softens the issue somewhat for me.

DR. MURRAY: Pat, did you want to add anything?

MS. BARR: I think I really tried to address it. I think it is problematic but I believe that this is a resource -- that our standards about ethics change over

time and that is a good thing. We continue to improve and become more thoughtful and more careful but that does not mean that what we do today should bar us from doing important things tomorrow. So what we did ten years ago or what our standards were ten years ago I think we would all agree are wrong but we should not then throw that resource out. We should find a way to use it if we can.

DR. DUMAS: And I also think that we should not eliminate the principle wholeheartedly, that we should maintain the principle that wherever it is possible and feasible we should have informed consent and that we should define as best we can the conditions under which we would operate when it is not possible or feasible in the case of accumulation of samples over a long period of time --

DR. MURRAY: Right.

DR. DUMAS: -- where there was no consent to begin with.

DR. MURRAY: And for me part of my own response to this question of how to think about samples that have been collected historically is in the considerations that Rhetaugh has really just described and Pat had described earlier but also in what we have gotten in the way of public feedback both in testimony in the kind of meetings that I have been reading the notes of that Pat -- many of

which Pat has participated in but also in our mini-hearings where we found -- I thought quite surprising -- support of doing scientific research and a concern about having the information if it were ever linked back to the person come back and hurt them and that, you know, the insurance companies are the villains of the piece by and large. That is what people mentioned spontaneously. But generally a sense that it is very much in keeping with Pat's conception and Courtney's notion of this as a contribution.

You should use it. If it is there and it might help people, by God, you should use it and that was key. So put all those together and I think it certainly influences my conclusions about how to treat those samples which we already have.

DR. DUMAS: They have to have principles.

DR. MURRAY: Pardon?

DR. DUMAS: Not you should use them but not without principles and some protections.

DR. MURRAY: Right. And now that we have been alerted to the significance, the potential significance of the tissue, we should not just -- we should not find past practices acceptable for the future.

DR. DUMAS: Right.

DR. MURRAY: And we should have a much more --

a much more serious consent process about potential use and I think we very much bear that in mind.

It is 12:15. We have --

DR. SHAPIRO: No, no.

DR. MURRAY: It is 11:45. I misread my watch yesterday. Excuse me. It is 11:45 by which I mean it is 15 minutes before 12:00 and I had promised Harold Shapiro that we would try to wrap things up about now so that he and I could say a little bit about next steps for this part of the report.

Jim, I know, wants to make a comment in general about the report and we may have -- do we have any public testimony?

DR. SHAPIRO: Yes, we have one person.

DR. MURRAY: One person. So we will need five minutes for that. But can we start with Jim and then I will speak and then Harold?

CONTINUATION OF DISCUSSION ON TISSUE SAMPLES REPORT

DR. CHILDRESS: Tom, you made reference to Courtney Campbell's contribution to this report with the notion of contribution and that this is -- one question I wanted to raise is to the subcommittee and the commission and Kathy and others who work on the report is really whether we want to follow the pattern of the plenary report

and have a separate session or even a subsection on religious perspectives? Because it seems to me that part of what Courtney's analysis suggests is that this is an area where religious traditions have not spoken out. They have not developed positions. And then he has to raise the question about how are we to interpret the silence.

It seems to me that it would be much better in this particular report to fold whatever points that come out of this discussion, the religious section, into the broader ethical section rather than having a separate religious discussion.

DR. MURRAY: I think that is how we see it right now.

Isn't that right, Kathy?

We just do not have the section on ethics discussion. We do not have the text there yet at least as I envision it.

DR. HANNA: We do not have the other half so we cannot merge them but I think that would be -- that is what we had been planning on doing.

DR. CHILDRESS: But the way it currently reads it looks as though it is going to be a section on ethics and then a section on religious perspectives. That is the reason for raising it. But if this is the direction then

let me affirm that direction.

DR. MURRAY: I think we agree with you. We would like to see it unfold as you have suggested.

DR. SHAPIRO: If I may comment just on this issue. I think we are in a very different position on this issue on this subject as Jim has just said than we were before. Not only have we heard substantial public testimony on that issue last time and we found out that these groups have been thinking a long time about these issues.

It is totally different in this case so I think not only should we merge it but it is not clear to me just which of these ideas at the moment are worthy of our inclusion. That is yet to be decided. It is going to be -- my guess is it will be a small subset of what is there. That is my sense right now but we will wait and see.

NEXT STEPS

DR. MURRAY: We have to decide what to do next now. Go out on a limb.

Clearly we do not have agreement on all points. We do not have full clarity on all points speaking today. I think, though, much of that is within our grasp. I wish we had another two days to spend together hammering out differences. We do not have that luxury.

What I would like to propose is this: That the staff of NBAC, those commissioners, not just subcommittee members but any commissioner who would like to have a hands on involvement in the preparation of the next draft, Kathy and I, work on the next draft, which we would like to see be -- I would like to see be a penultimate draft and be pretty near final.

Now that may mean leaving certain things in brackets where we still have a few decisions remaining. It will certainly mean some points that we think we made clear will not have been made sufficiently clearly for all members.

It has been further suggested by Eric Meslin, and we talked about this in subcommittee yesterday, that we see -- at some point see a draft of the report, either it would be the next one or perhaps the one after that, and post it as an interim report and actually post it on the World Wide Web for public comment for a period of days, perhaps 30 days, before we then can take the comments and assimilate them and decide what changes, if any, to make in what will be our final report.

I would like to see all this happen expeditiously because you can draw these things out and make them a little better but again we would like to see it

happen in our lifetimes. In fact, I would like to see it happen early in 1998 as a final report.

So, I guess, my proposal, and I would like to hear Harold's response to this, is that we have a very ambitious second draft of the report which we hope will be either the penultimate or the near penultimate version of the report.

DR. SHAPIRO: Thank you, Tom.

I think we have decided, as Tom just indicated, to take the first draft that we are at least almost satisfied with and issue that as an interim report, wait for some comments like 30 days, and then with our own analysis go back and see if we cannot produce a final report.

I would say, Tom, there is a big area between 30 days and our life times, I hope. So we will have to see just how much time we have there.

But I think we will spend a large amount of intensive staff time on this report in the next month and it would be extremely helpful to us and to the quality of what we are able to do ourselves if those of you who have, one, challenging ideas that you think need careful consideration if you would write them down so that we can analyze them as carefully as possible because we will make

every attempt to respond to all the issues raised here today one way or another, either by clarification, changing the nature of the recommendation or the structure.

There are lots of different ways of responding. That is not to say that every point can be gotten then because there are some that are mutually inconsistent and we will have to make some choices but those will be argued out by the full commission itself at our next meeting where those occur.

Perhaps the vehicle Tom has recommended where we see those happening we can think about some alternatives and include them in the report and we will have to argue them out as we meet.

So I see the next month to have, one, very intensive staff work on this. We will have to call on particular members of the commission during this time to help us out to perhaps writing a few pages or by clarifying or helping us think through issues. I think you can expect to hear from Eric and/or myself and/or Tom in the next weeks as we try to move ahead. It is not that long until we have our next meeting.

As you know it is less than a month so it will require some intensive work but we ought to take that on as an objective. If we do not quite make it we will get as

close as we can. So I think that is entirely acceptable.

Let me -- we will have to move on now. Let me say something first of all about this afternoon's agenda before we go to public comment and then take a break for lunch.

I noticed on our agenda we meet for three-quarters of an hour and then have a coffee break. That seems a little excessive so I have decided that we will eliminate that 1:45 coffee break and go immediately at 1:45 to the report on Human Subjects Subcommittee. We will try to move from that to the federal oversight item at 3:15. Again 15 minutes ahead of where we were.

And if discussion allows we will try to go to processes in changing regulations at 4:00 o'clock. It may be that three-quarters of an hour is not enough. We will have to see. If we do that it will enable us to finish somewhat earlier than is indicated here, which would help a lot of members of the commission, including myself, so that we will try for that. If we do not -- we do not

want to inhibit the discussion, if we cannot make it we cannot and we will just go a little bit longer.

Are there any other questions before we move -- we only have a minute or so before we have to move to public comment?

DR. MURRAY: Can I just on behalf of the Genetics Subcommittee thank our guests today very much and thank the other members of the commission for taking the report seriously and giving us lots of useful feedback.

DR. SHAPIRO: Let me just add one other thing. I know many of you have done editorial and other comments on the draft that we had. Please do not forget to give those to Eric, myself, Kathy so we can have them and take a look at them and consider them.

Okay. Thank you all very much.

I believe we have only one person for public comments.

Is Mr. Rabin here?

Do you want to come forward and use the microphone, please?

I also want to remind the commissioners that Mr. Rabin has submitted some written materials which was in the book that we all got.

Mr. Rabin, let me remind you that the rules that we have here is five minutes. Thank you very much.

STATEMENTS BY THE PUBLIC

MR. RABIN: My name is Norman Carl Rabin from Plainview, Long Island, New York. This public statement by the way is --

DR. SHAPIRO: Hold on a second and see if we can get the sound improved somewhat. It is a little hard to hear. Talk as close as you can to the microphone, please.

MR. RABIN: Okay.

DR. SHAPIRO: That is better. Thank you.

MR. RABIN: I am not experienced with microphones.

DR. SHAPIRO: I know it is a little uncomfortable and I apologize but it is easier if you get very close to the microphone.

MR. RABIN: Okay.

This public statement is accompanied by a 15-page document fax that I sent to the commission last week.

My name is Norman Carl Rabin from Plainview, Long Island, New York. I am a victim of illegal nonconsentual U.S. classified research type activity for over 12 years. After innocently reading a mathematics paper as part of employment I was covertly assaulted by U.S. government satellite space assaults in 1986, 1987, 1989 and 1990.

Since October-November of 1990 I have literally been held a prisoner of advanced technology, multiple satellites monitor and assault seven days a week, 24 hours

a day, even while I sleep. Since January of 1994 I have gone to other victims of this type of crime and I now know of about 35 other victims of monitoring and/or assault of their body.

Picture three, or four, or five more stationary research type satellites utilized to monitor and assault and track each such victim 24 hours a day. In all cases each such victim is targeted illegally and without consent by the high technology use of electromagnetic signals to monitor the person's thoughts and/or actions and in many cases to assault the person.

Again I have literally been held a prisoner of multiple satellites monitor and assault for over seven years and two months in spite of my complaining about it and massively publicizing this crime.

Besides from the murders which the U.S. Government has certainly committed around me and besides from the torture or other cruel and unusual aspects, the worst part of the crime against me is that it is a blatant violation of the U.S. Constitutional Fifth and Fourth Amendment guarantees of liberty and the security of one's person. Moreover, now over the course of 12 years my own life has literally been ripped away at by the lawless, month after month, year after year, with the assistance of

the U.S. Government to do this evil crime against me.

I was 25 years old. Less than two years and eight months out of college when this crime began. Last month I turned 37 years old. To steal a victim's life for years on end is an evil crime and to steal years and years of a victim's youth is decidedly a worser crime.

I know other long-term victims. Victims targeted for ten or more years and I see the wrong -- the evil which is going on. Human beings deserving of human dignity and even in all cases even respect are not to be treated this way. Humans are not to be treated as subjects of machine operations for machine oriented projects of any type. This mangelesque, i.e. a denial of humanness for years or even for months if each of you would think about it for a few moments.

The problem with this crime is loophole which evil doing persons have exploited. They are doers of crime under secrecy and censorship.

As I have recorded in the following statement in my now public formal June 2, 1997, letter to Senator Glenn on S-193, the proposed Human Research Subjects Protection Act of 1997.

"

I urge the U.S. Government to support a U.S.

law or constitutional amendment which would expressly endow citizens with the right to be protected from crime committed under secrecy and/or censorship. Any monitoring society having secrecy in science and technology needs this law. Please help with this proposal and its passage.

"This type of law is a normal and natural step in the progress of civilization. This law should have power to use the public justice to stop crime under secrecy and with other victims to get lawyers who now have a U.S. law to work with. U.S. judges should gain the right of inquiry under seal to any crime under secrecy."

In an age of science without this law our country, our United States, is not a free country. Let this commission tell it like it is, our country needs the explicit right to be protected from crime by anyone where that crime is committed under U.S. secrecy and/or U.S. censorship.

Thank you.

DR. SHAPIRO: Thank you very much.

Any questions any members of the commission have?

Thank you and thank you very much for taking the time to come and thank you for your written testimony as well.

We will adjourn now for lunch and ask you all to please be back here by 1:00 o'clock, not 1:05 but 1:00 o'clock.

(Whereupon, at 12:01 p.m. the proceedings were recessed for luncheon.)

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A F T E R N O O N S E S S I O N

DR. SHAPIRO: I think we should begin now. We will have no chance of completing our schedule if we do not begin now.

As you know, although the first priority of our work is to continue and finish the projects that are currently under way, we have begun thinking about our longer term agenda and I asked Eric Cassell to speak with a couple of committee members to give some thought to what items might appear on our longer term agenda so at least we can begin thinking about them and thinking about mobilizing ourselves for them.

I will also be speaking in the next four to six weeks with various members of the administration and the Congress to see what is on their minds that might -- that NBAC might do that might be useful for them and will feed that into our own considerations also. So this is not an item that needs to be decided today. That is we are not about to take any decisions. This is just the beginning of the discussion which will probably occupy some time in all our meetings in the next two or three meetings until we can focus down on some things we want to do and some ways we may wish to organize ourselves.

So let me turn now to Eric and let him describe

to you at least what the initial considerations were of the members of the small group which he met with. I think you had a telephone conference if I recall.

FUTURE COMMISSION RESEARCH ACTIVITIES

DR. CASSELL: Yes. We have to use the microphone Chanteuse-style.

Your committee for this was Alex and myself, and Alta Charo, and David Cox, and Eric Meslin, and Henrietta Hyatt-Knorr, and so it is Eric M. and Eric C. now on e-mail so that we distinguish each other.

We divided our concerns into two. One was -- one had to do with commission process and the other with actual program suggestions that we thought might be useful.

The first part of it was we thought there was considerable sentiment for not breaking up into two large groups and meeting separately again. We are by my own experience and other people's reports a very congenial commission and we get a lot of work done around the table and we have a lot of different talents, and we thought we really would do better if we could try and stay together. There are some days maybe that is not possible but in general we thought that might be a helpful matter.

In addition to that there was also sentiment for having longer meetings less frequently. We have a

meeting monthly and we are hardly finished with one meeting and then we are already into the next and we are really not quite ready, we thought, so we hoped we could prevail on our chair to consider possibly changing our schedule somewhat. We thought we would be more productive if we did that. These are all matters for discussion.

But there is another aspect of the same thing and that is we are -- when we did the cloning report we were -- we did not have the amount of staff that is usual for a commission and so here we are we were all commenting on drafts that had not yet become drafts and they went back and forth, and in and out, and then -- a very unusual way of writing a report. It has to be one of the most unusual way in writing a report that I have ever seen.

Whereas, we now have excellent staff and staff in-depth and we thought that this would also allow for a much better use of staff, all of whom are really expert now, to circulate drafts, to make proposals, to do the research so that we have something in hand and we are working on that before we get to a meeting and even as was just suggested a lunch so that we are at several levels. We are hearing one thing that is maybe ready for a couple of meetings down the line and another thing and so forth. And that is something that we are able to do now because of

the richness of staff which comes from other more direct richnesses.

There is some question about whether we have to have one kind of report. Whether, in fact, the reports that we now circulate among ourselves in draft form -- is there a reason for circulating those reports publicly? I think they are part of the public record, aren't they, so that, in fact, anybody who wants to comment on them could do that by testifying in front of us but there might be reason for having public comment on drafts even that we circulate outside and that would enable people who cannot come to our meetings to make comments and allow us to be enriched by those comments.

We also might -- and this is an issue that allows us to decide, well, what do we actually do. We have a policy assumption. There is no question about that. We are to come up with public policy but by the way we are constituted and by our natural bents we also have an academic function. Does one kind of report meet both those needs the best? Are there things that we might do strictly as a policy recommendation report and other things where we want greater depth and background and greater academic depth because we know we are talking to the bioethics and scientific community in a different voice than we might do

to policy makers?

We also -- some of my committee members felt that we have not clarified yet what kind of a commission we are, whether we are primarily a regulatory -- suggest regulation and policy or whether we are a standard setting commission, or whether we are a problem solving commission like the Institute of Medicine does, or whether we are a reflective research organization which is related to science because that is what our mission is but on the other hand we are able to bring to that a somewhat Neitszchean understanding that there are other issues and uncertainties and troublesome things in the world and moral life that a commission like this is meant to reflect on and bring back into the scientific world. We thought that we might well be able to do that.

A somewhat similar matter is the question of whose ears we speak to. Do we speak to the President? Are we speaking primarily to legislators? And I think Harold will be able to, if he wishes to, address that more directly. Just who are we talking to? And must we -- in that same sense are we only one thing, which is the same as I said earlier.

Now, I think Alta Charo felt that because we had finished the cloning report and we are getting out the

stuff we are in now that this was a good time to reflect about how we saw ourselves as a commission.

My own sense of watching from the outside is that we have -- we are being successful in the way commissions work and that gives us a bigger chance to self-define and write a ticket, an intellectual ticket which most commissions do not get a chance to do because they are having too much trouble fighting with each other. We ought to take that -- and I think Alta is correct about that.

So let me pause for a moment and then go on to what we -- what was really our goal as far as a committee to see what program items we might come up with rather than deciding we need a new garage or whatever.

We thought that as we discuss this in our telephone conversations jointly and separately, though I must say because of me we really did not have one large conversation or one large conference. I could not make the one we were supposed to have because my medical students and my office staff were having Christmas parties and I was not going to be very functional.

We thought that we ought to make a distinction between larger and what we call big ticket items. For example, the problem of the ownership of the human body, which we will come back, and I put here smaller but I do

not really mean smaller as much as more sharply focused, such as those concerned with IRB function. And I do not think we want to see ourselves doing solely the latter, should IRB's do a new structure for IRB's or new regulations but we would like to see us doing both these kinds of -- taking on these kinds of problems.

However, we do have immediate concerns that we think should at relatively center stage. The first of these is the Institutional Review Board problem. We mention it again and again and again. It comes up. We are dissatisfied. Every one of the problems which we heard in the testimony on the decisionally impaired subjects also had a failure of an IRB and a failure primarily because of lack of education or structural concerns.

So it is very hard for us not to take -- should this still be the way moral concerns in biomedicine are handled and, if so, are there changes to be made so we ought to take on that directly. Also, it seems to be ideally -- subject ideally suited for the staff level we have been talking about where the background research can be done. We can set up studies that might have to be done and then come in with something which would be a basis on which to make decent decisions.

There is another question which is in the

literature at the present time and that is the ethics of research done by United States investigators in other countries. We all know that the transmission of HIV was addressed in studies done in Africa not using placebo -- or using placebo controls in a fashion that would never have happened in the United States at this time and rising an outrage, which is a very simple posture, a very easy posture to take, rising an outrage for editorialists at the New England Journal .

Marcia Angel is wonderful but there is greater depth that could be brought to that problem than has been brought so far and we are the people, I think, that could do that. While it is important to address it, in a funny way we are back to the Ugly American problem in reverse. Right after the Second World War and across national boundaries medical care we were one thing. Here we are again back to that same problem and it is an interesting one and worth review.

There are people incidently who will be very happy to testify in front of us good people and hold sharply different views.

The privacy and confidentiality issue in genetics and the whole issue of privacy and confidentiality is back in front of us. We have been dancing around it

today. In our first meeting or two we had some exchange about it. I personally feel that it is unsolvable at the present time. The problem of how to solve confidentiality in medical care and medical records is -- I cannot see how to get a handle on it.

On the other hand it is possible for us to take up a problem not so much with a solution in view as with a way of delineating this is what the problem is, it is in these different kinds of situations, and we have done it when we have laid out the problem. We can now step back from it and let there be public debate about it as we have laid it out.

There is an interesting -- opportunity is offered by the fact that the 20th anniversary of the Belmont Report is coming up in April of 1999. So the topic that you will find listed in this report is the Belmont Report Revisited.

An in-depth discussion of the adequacy of its conceptual framework or -- adequacy is not right. The changes in its conceptual framework of the paradigm shift that has occurred since 1979 in the latter progress in research ethics and the public consciousness. As I note, it would be a good thing to see this happen and come out at the same time as the anniversary. I have a personal thing

that I am supposed to be writing something about the change over those 20 years and this will allow me to put it off yet for another -- anyway I think that is a subject that we might give consideration to.

A number of us feel very strongly about the issue of education. This has come up repeatedly in relationship to the knowledge that IRB members bring to their work and to the failures of investigators, the young ones and more experienced ones, because they simply do not know enough about research ethics or ethics in general. The media is very poorly informed about issues of ethics and policy makers, legislators and the public at large. There is not only the issue of ethics. It is the issue of science education in general that came up through the cloning report.

We think that this again is an area where staff background -- and we begin to find out who is doing what. What foundations are out there who have money to do studies on education? What government bodies are doing it or think they are doing it and so forth? Just as in other areas we think we have to lay out a fair amount of information and background studies before we tackle it but we feel very, very strongly about it.

Bette Kramer and I spoke about it earlier today

and she may want to comment.

And then there are some other problems that have been mentioned. Gene patenting, bioethical issues in behavioral research. I have these lower down on the list because there is limit but behavioral research does not fit well into the biomedical model. It has always had discomforts in IRB's and yet an alternative is not clear. And then there is compensation for research related injuries which also keeps coming up and subsiding back down again. I think because nobody can figure out what to do.

There are larger areas. The right to health care. The previous national commission articulated the successful -- previously successful one -- articulated years ago that there was a -- that the nation had an ethical obligation to ensure equitable access to medical care. It is now 20 years later. Lots of things have changed. Inequity persists and grows, in fact, and while it is a problem there is a question of whether we should take it up and if we took it up towards what end and what resolution, and what will become out of it.

Alta Charo raised the question about the interesting issue about who owns the body as a larger question. There are major cultural differences in what your relationship to your body is in terms of ethics and

the law. In Orthodox Judaism you do not own your body. You have not got the right to refuse resuscitation. It is not your's to refuse. The Mormons are also the same way. You do not -- you inhabit, you are a guest in the body and the body is God's. Those are just two of the views.

I think most people are very confused about how they feel about their body on whether they own it or not or whether it is an it or a them, and yet those matters have direct bearing on tissue samples, on the consent to research, on legal issues that are poorly resolved that we might take up.

And there is a question I have listed here called the limits of clinical care.

It has something to do with the issue of progress actually, Zeke, that we talked about before.

There is no question that there has been enormous progress in the resuscitation of newborns who previously would have died, in multiple births where previously there would have been no survivors we now have the septuplets, and yet we do not have any real idea of what about the others. What about the kids who did not come out and go on and become the president? Of their class of course. And what about the other ones? What has happened to them? What social resources are used? What

are the obligations society has to them? They are a sort of byproduct of progress. In fact, if we saw it all laid out we might not think progress was so wonderful in relationship to them. The same thing with the multiple births.

I am struck by the number of elderly or old elderly. They are now called people in their -- in late '80s and '90s who are extremely functional. I have numbers of patients I look at and I wonder how come you are alive. What are you doing alive? And I know why they are alive. They have a cut down the center of their chest. They have had an angioplasty or two. They had a carotid enterectomy and they are out there and functioning.

But not every one of them made it and a lot of them ended up in intensive care units for long periods of time with nobody knowing how to stop it. That is also an issue that might be taken up and begun to be explored because I promise you physicians do not have the faintest clue about how to stop those things unless they do it covertly. Yet we sure do know how to start.

So those are some of the issues.

Finally, as the very last one, and for good reason, I have reproductive technologies. I put it last because I think that it has so many pitfalls that until we

have more muscle as a commission, until we have been more successful and maybe more callous is a good way to put it, I think we might be careful about stepping in there where there is so much can happen in relationship to the public.

That is our report.

DR. SHAPIRO: Well, Eric, thank you very much and thank the others who participated in outlining some of these issues for us.

I am going to turn to the commission in a moment. We have perhaps 15 minutes to discuss this or give initial reactions. As I have said, we will read new versions of this as we go along and gradually hone in on an agenda.

Let me just say a word about the process side. Perhaps the easiest to resolve and perhaps even the least important.

First of all, as you pointed out, having the staff we have now it would be perfectly feasible for us to meet as a group generally and to meet for longer times less often. I am very sympathetic. That is a lot easier for everybody.

I just wanted to note that in attempting to put together our calendar over the last few years it has been almost impossible to find two days we could get a majority

of the commission available, any two days, so that I am perfectly willing to try. I think, in fact, it is a good idea. I accept the notion it is a good idea to do that. We will give that a try if others on the commission agree because I do think, myself, it is a very good idea and a better way to go about it. So I accept the recommendation speaking personally.

If other members of the commission agree we will just go ahead and try once more encouraging everybody to really make an effort to help us out and give us the two days when that is necessary but I like the idea in general.

Regarding -- I will just give you my own personal reaction regarding the nature of the reports. I do not think, myself, and I think that was the tenor of your remarks if I understood them, that there is any need to decide on one versus the other. I think we are going to speak in different ways at different times and different kinds of reports depending on the subjects and perhaps even the different audiences.

So I much prefer, myself, to preserve flexibility in that respect and focus on the problem and decide given this problem who should we be speaking to first, in what way and in what format, and so on and so forth.

I take it that was really the committee's view also.

DR. CASSELL: Yes, that is our general feeling.

DR. SHAPIRO: But maybe we could start off with the easier part of this and just address what Eric has referred to as the process issues if I can phrase them that way and see and just get a general sense if people would. To take a specific item I would like to meet for longer times but a fewer number of meetings. That really means two days every second month just to take an example rather than one day every month as another example.

How do people feel about that?

COMMISSIONERS: Yes.

DR. SHAPIRO: Let me ask an easier question. Does anybody dissent from that?

Okay. We will give that a try. Please make an effort to be helpful to us with your calendars and we will look at this year's schedule because we do not feel -- I do not feel committed to it. We can easily cancel a few meetings this year and make the ones we have longer. We will be back to you. Eric and the staff will be back to you on that issue.

DR. MESLIN: If I may, though, it might be useful before we leave that question to consider whether

you do want to meet next month, which we had tentatively asked you to put on your calendars. A meeting that was scheduled to be in Los Angeles. You have heard from this morning's discussion that there is a strong desire to get a high quality research product out to you, the stored tissue report, and I suspect you will hear a similar sentiment this afternoon and after tomorrow's subcommittee of the Human Subjects Committee on the report on subjects of questionable decision making capacity.

You may either want to speak now or think about this and speak fairly soon because we have made some tentative arrangements to meet in L.A. sometime around the 5th or 6th or 6th and 7th of February. It may turn out that it would be easier and make more sense to forego the February meeting and meet in March, which would give us two months to produce the kinds of things that we have been talking about.

So I just flag that for you to consider.

DR. SHAPIRO: Steve?

DR. HOLTZMAN: Do we or do we not also have on the schedule a meeting on the 23rd of February?

DR. MESLIN: We do not. We had asked you to reserve a couple of dates in February and the date that we

had more firmly settled on were the earlier dates.

DR. SHAPIRO: Carol?

DR. GREIDER: I would like to address the issue of the February 6th meeting. I feel like at least for the Genetics Subcommittee there are a number of issues where we have put off discussing substantive components of putting in specific recommendations in specific boxes in our matrix that we really have to discuss before we can write a report. We do not have the substance yet of a number of those important issues and so I think foregoing a meeting at this point would not be productive because we cannot be doing work in the meantime to write up our reports if we do not have the answers to what we are going to recommend.

DR. SHAPIRO: Let me -- let's not try to resolve this sitting here right now but we will over the next day's interaction with members of the committee and the subcommittees decide specifically about the February meeting. We may do everything from have a full commission meeting or if that does not seem desirable and it does seem desirable for the genetics group to get there then we might have that. We might cancel both depending on what is decided and go to March.

We cannot avoid dealing with the question that you have raised obviously but let's not try to settle this

here. I do have the sense that at least we should try to structure our meetings going forward to the extent that is possible and feasible around roughly day-and-a-half meetings half as frequently as we currently plan.

Okay. That is very helpful.

We will go ahead and try to organize ourselves that way if we can.

Let's go on. There are other issues which we can come back to on process but I think that was perhaps the most important of the ones.

Let's go on to the issue of program and the various suggestions that Eric made and let's see if there are any members of the commission who have any reaction to that.

Arturo?

DR. BRITO: I just wanted to make a comment about general functions as something that Eric mentioned.

I thought that we had decided during the cloning report that we were not a regulatory body and maybe I am confused, maybe we just decided for that particular topic. But you mentioned that one of the issues is that -- what is our function and I thought we were more of a suggestive body basically depending on what audience we are making suggestions to but not a regulatory. Has that been

-- there has been a change of heart amongst some of the members or you just want a clarification?

DR. SHAPIRO: No, there has not. Even if we wanted to be, we could not be, but I do not think -- my sense is no. I did not interpret the comments Eric made that way. I interpreted them as the question of whether we should be suggesting regulation to whoever the regulatory bodies are but that is how I interpret what Eric was saying.

DR. BRITO: Okay.

In terms of the specific topics I want to say that they all sound very apropos obviously but it would be very ambitious to tackle them all. One of the ones that is very focused that I think we should tackle right now and has been raised before is the research being done by this country in other countries, particularly pharmaceuticals particularly with the HIV studies because I think there is a lot of room there where we could contribute both pro and con and reasons for placebo and not placebo, et cetera. I think that is something we could tackle in a short amount of time and do a reasonably good job.

Then the education I think is also very important to do because I think there is a lot of misconceptions about suggestions we make or other bodies

make particularly from the media and I think that is where we should start with the educational process.

And then the behavioral research. We had mentioned before, and I do not know if that has just been lost somewhere, about addressing the issue of research with children or involving children. I think this is where maybe we could tie it in particularly because I think there is a lot of problems with behavioral research lacking in children for various reasons so I think that is where we may be able to tie that in if we decide not to address that specifically at this point.

DR. SHAPIRO: Thank you.

Jim?

DR. CHILDRESS: I very much like the list of immediate concerns and I think I would also note that several of these the Humans Subjects Subcommittee has raised at different points as important for us to cover. I would also mention that a few of these may have a higher status than this indicates. For instance, gene patenting, as I recall, was one of the things we were asked to look at by -- perhaps even in our charter.

DR. BRITO: The President, yes.

DR. CHILDRESS: Certainly the -- I think one of the documents that established us. So one question would

be whether we need to give that greater attention.

In addition, the Institutional Review Boards discussion is one that we have been holding off until we can get the materials from the two studies that are underway but the document from the Clinton Administration on Building Public Trust indicated that we would make a report on this within a year. That year is now passed but it is certainly something I think we need to attend to.

The Belmont Report Revisited I think is a great opportunity for us to think through, particularly in relation to a concern that Zeke Emanuel raised at our very first meeting, whether these principles are too individualistic and perhaps need to incorporate greater sense of community. This is something that runs throughout our discussion of human subjects research as well as the tissue samples report. I hope that we could do that over the next year.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I also like the list a lot. I think it is very rich. I would like to pick up on something you said, Eric, in terms of what is the audience we are aiming for. What is the opportunity to change something, whether it is policy or just the way people look at a problem?

I guess I would ask the question a different way. Where do we have an opportunity to make a difference? We could write a really nice report but where is it going to make a difference in terms of changing policies, changing practice or changing how people think? Is there a group of people out there that want to hear what we have to say?

So far all the things we have done we have been lucky in that the audience was preexisting so people wanted to hear about cloning. There are a lot of people who want to hear about stored tissue samples. There are a lot of people who want to hear about research on people with questionable decision making capacity. I think it would be nice to pick a topic where there are some people out there who want us to say something and are likely to at least listen to us even if they do not follow our advice.

DR. SHAPIRO: Thank you.

Other comments?

David?

DR. COX: So Eric spoke for me in a way being a member of the group but I would just like to say that out of all of these the one that is highest for me is this revisiting the Belmont Report. I say that because as the National Bioethics Advisory Commission that if we can look

and ask what the foundation of this country's bioethics -- if it has changed one way or another then that is an extremely important task. So I am -- it is a favorite one of mine.

DR. SHAPIRO: Let me make a comment about that particular one as I have thought about it, that is the Belmont Report 1999, I guess is it's -- right, was it '79? Yes, 1999. That actually is around the corner in terms of doing something thoughtful and meaningful. We can devote a certain amount of time to that because I think it is so important but we will be limited in the amount of time.

What I thought about in terms of that is we might take the lead in sponsoring some work in that area, whether it is a volume of essays or whatever it is, we could work on it, to which some members of this group may choose to contribute as opposed to issuing a so to speak new -- that is not what was suggested -- Belmont Report. Those are the things I think we have to think through but I agree with you, David and Eric, and the others who have thought about this that we should not let that event pass without some kind of event, some kind of response. I think that is right.

Yes, Bette?

DR. KRAMER: I would hope that with all the

specific subjects that we address that we will not let go of this factor of education. I think Bernie just mentioned where is the audience. Well, I think it is incumbent upon us to seize the opportunity that we have and the obligation I believe we have to enlarge the audience. The only way we are going to be able to do that is by providing or fostering some educational efforts.

I think that Eric mentioned that he feels the issues of privacy and confidentiality are insolvable at this time and that what we can do is lay it out. But insofar as we do not enlarge the audience to whom we are speaking it is not going to be helpful.

DR. SHAPIRO: Thank you.

Let me ask a question of Arturo.

Arturo, I did not quite understand what you were referring to when you referred to research with children or involving children and you tied that to behavioral research in some way. I just could not quite articulate or draw in my own mind exactly what kinds of things you were thinking about.

DR. BRITO: Initially we decided not to address the issue of children, research in children, because there are regulations in the Common Rule that are somewhat vague but they are there.

DR. SHAPIRO: Right.

DR. BRITO: And we went just with decisionally impaired.

Then in discussing -- but in the context of discussing that we have discovered basically or I have discovered or some of us have discovered basically the main issue right now, the main criticism of research that involves children is that children are not being included enough in mental health research, behavioral research, because the regulations -- at least in this country the regulations are, although vague, they -- research has not attempted to involve them in that because of the risks, et cetera. And that has become questionably unethical in itself not to include children.

So I understand from behavioral researchers that maybe --

DR. SHAPIRO: Maybe one of the things we could at least consider is revisiting the existing regulations regarding the use of children and see whether those could be expanded, changed, reshaped or somehow supplemented in ways that would be helpful but okay. I just was not clear exactly what you were suggesting.

All right. Let me suggest that what we will do is -- this will be on our agenda every meeting. Probably

not for an overly lengthy period of time. But we will come to our next meeting whether it happens to be in February or some other more distant date with what we consider an update or some suggestions that are associated with each of these, dropping some, adding some, and we will just contribute to the discussion and see where it takes us.

Is that satisfactory to everyone?

Okay. Thank you very much.

Let's go on to our next topic, which is the report from the Human Subjects Subcommittee regarding decisional impaired and people with questionable decision making capacity. This is subject, of course, we have visited at enough numerous meetings. Now we have a report.

I want to thank Jonathan again and others who contributed to it. Jim and others who contributed to that. At least my own observation is that each one of these drafts has made important improvements and are very responsive to a number of issues raised here so I want to thank you, Jim, for that and thank Jonathan and others who have worked on it.

So, Jim, let me turn to you now to sort of take us through this discussion.

REPORT FROM THE HUMAN SUBJECTS SUBCOMMITTEE:
RESEARCH WITH DECISIONALLY IMPAIRED SUBJECTS

DR. CHILDRESS: Thank you. I would second your expression of appreciation to Jonathan and now to Eric, who has joined us, but also to members of the subcommittee who participated very helpfully in this process.

I would like to have one item passed out. It is a response I just received this morning from the National Institute of Mental Health to the November draft of the report. Enough copies were provided to make available to everyone.

Let me offer my comments under three headings. Why, how and what, or a priority processing of the product if you prefer the latter.

Why? Why did we give this topic priority? It has been on our agenda since the very first meeting of the subcommittee last December a year ago and then it was added to the commission's agenda as a whole at a subsequent meeting.

Why? There is a long history of discussion of this particular set of research subjects, particularly following the work of the national commission whose recommendations of special protections were not adopted. Many researchers, many subjects and their families, believe that additional guidance is needed to make sure that subjects with questionable decision making capacity

are adequately protected and also to ensure public trust as essential to enable appropriate and valuable research to go forward.

There are various proposals in the literature. For example, if one looks over the last two years at the large number of articles on this topic with recommendations of various kinds of guidelines.

How? How do we get to this point and what process we are following? Well, we have heard from a number of investigators, subjects, families of subjects, policy makers, commentators and others, both those who were invited and those who volunteered to contribute either written materials or public testimony. Certainly one valuable session, very valuable session was the large public hearing we held in mid-September.

In addition, we have had contract papers from Rebecca Dresser. A very large and helpful paper that then Jonathan Moreno used as a basis for the draft that you have before you. A draft that has gone through several different versions already.

In addition, you will be getting later today -- there was a confusion bout whether we could get copies made and when -- a few additional pages prepared under contract with Paul Appelbaum to go into those sections in Chapter 1

with appropriate modifications having to do with the different disorders that are particularly relevant to our discussion and the promise of research in this area.

In addition, we are exploring the possibility of another paper looking at measurement of competence, kinds of value issues lurking in that discussion. And also a literature search on research involving greater than minimal risk. These are things that we will come back and discuss.

Another important part of the process is attending -- several subcommittee members attended a National Institute of Health sponsored inter-institute conference looking at possible guidance for investigators and IRB's in the area of research involving subjects with questionable competence or questionable capacity. This was a very important meeting.

A report will be coming out of that by the end of the month and we will make that available to everyone. But those of us who participated in the meeting were able then to make recommendations for the revision of the draft and the draft you have before you includes in bold a lot of those additions as well as other additions that were made and suggestions not only from subcommittee members but from other commissioners.

What do we have? What product? Well, as I noted this draft builds on all the written and publicly presented materials I noted.

There are problems. We think it has made -- we made considerable progress with this report but as people who have read it within the commission and outside have noted one of the big questions that arises is whether we have established an adequate connection between the first several chapters and the conclusions and recommendations. I think all of us agree, no, we have not done that.

One important possible contribution of this meeting would be for us to get clear about the kinds of recommendations we want to make because that would then lead us -- give us a way to restructure the report. I think much of the analysis, thanks to Rebecca and Jonathan and others, is in very good shape but now we really need to know how to structure this depending on the recommendations that we want to make.

So I would -- I guess another aspect of that would be how much we want to recommend in terms of regulation and how much we want to recommend in terms of guidance. So one strong recommendation from the NIH conference in early December was no more regulation but we are actually in the current draft proposing regulations and

we need obviously to keep that in mind.

Well, let me stop there and see if there is anything Jonathan would like to add and then we will open it to discussion.

DR. MORENO: Just very briefly. On page 150 on my copy the final line is missing. It was dropped between my computer and the NBAC distribution process. The word "and" appears on that summary of recommended framework. After that word "and" should be the phrase "health care professional monitor." It is reflected in the text but it did not -- it got dropped. That last line got dropped.

DR. CHILDRESS: Say that again, Jonathan.

DR. MORENO: Sure. The last line in the summary of recommended research on page 150 in the right column you will see the word italicized "and" which is followed by nothing.

DR. CHILDRESS: Right.

DR. MORENO: I did not mean that to be a fill in the blank test for members of the commission. It occurs to me at this moment that might not be a bad idea. The last line should read "and" and the last line is "health care professional monitor."

MR. CAPRON: Health care professional monitor.

DR. MORENO: Health care professional monitor.

That is not a monitor for health care professionals. That is a health care professional to monitor research with respect to the well-being of the subjects of research for this category of research. This is reflected in the text. It just got dropped from this page.

That is all, Jim.

DR. SHAPIRO: Jim, why don't -- if there are any comments any of you have let me turn the chair over to Jim for the rest of this discussion.

DR. CHILDRESS: All right. The floor is open for discussion. Again I would like to have all of the suggestions you have for the revision of the report. We do not have a lot of time so some of those you may want to submit by e-mail. I think it would be particularly helpful if we could look at some of the recommendations, the ones that are given here, and the kinds of modifications you would propose for them. That will help us then think further about the revision of the report.

DR. EMANUEL: Jim, in this summary of the recommendations there is no potential benefit, no potential benefit issue, and the use of advanced directives. I have for reasons you and many others in this room know about serious concerns about that as an operative principle. We have a lot of data that it does not work in other areas.

We are now going to import something which does not work somewhere else into this area and I am concerned about that.

I think the intention is understandable and right but the potential operation is likely not -- for lots of reasons not to meet that. So I am not -- I think this is a very important step that, you know, needs elaboration and consideration. I am very unclear as to why it is there.

DR. CHILDRESS: Thanks. We will get response from others.

I share many of those reservations, as Tom mentioned, regarding the report this morning. This is a work in progress and the fact that it appears in this form does not suggest or should not be taken to suggest unanimity among the subcommittee members about particular matters here. So this is one that is still under discussion.

Eric?

DR. CASSELL: I just want to register I share the same concerns.

DR. FLYNN: Could we hear --

DR. CHILDRESS: Laurie?

DR. FLYNN: I do not mean to interrupt. I just

would benefit from hearing a little bit more discussion from Zeke or Eric as to the concerns they have seen in other areas and the dangers they see in trying to import this into this arena.

DR. EMANUEL: Well, I mean the sort of end of life area where the advanced directives have had the most run for the money. There are a number of problems which have been identified. Failure to fill them out. Failure to understand what you have filled out. Failure to implement them at the appropriate time. Questions about stability over time. And I think relying -- and they have never been tested in the area of research. They have been -- I mean, we have looked at them in an area that has a lot more salience maybe for people.

I think as a mechanism we have had, you know, maybe 20 years of experience with them and I generally think the conclusion in the field even by myself, who is an ardent advocate, is we trusted them too much. At best they are part of a process. And we end up, like many things, relying on a document that does not seem to reflect the process. Most people do not use them even after extensive publicity. I mean, it is hard to understand how much publicity. You know, most people do not do it even if they want them.

So it is -- I mean, I think as we heard from the people in the New York group the idea that people are actually going to do this is, I think, clearly unrealistic. You just have to understand that if you put this into place you cannot have any greater hope than five or ten percent of people are ever going to do this. I think we must be very clear about that.

It is not because only five or ten percent of people may want to participate in research. I mean, if there is anything we know, there is a big gap between attitude and action here.

DR. CHILDRESS: I have Eric and then Alex.

DR. CASSELL: And then the other issue of it is then they are not heeded. The evidence shows that then the people for whom they were written, that is the physicians in care, do not pay attention to them.

Now the conclusion that is usually drawn is that is because they are bad guys and they do not want to pay attention. I think that is not it at all. They do not know how. They do not know how not to treat. They do not know how in this kind of thing to apply a directive written way ahead to a piece of research which will not really precisely the way it was that that directive was written for so we have this problem.

There is another aspect of this which is we keep talking about more communitarian view of what the process is and then when we come to write a recommendation we are right back to trying to do it as though there was no community whatsoever and we have not protected this person totally against without having put some kind of standard in that would allow the research to go on and protect the individual.

Now, I do not know -- you could come back to me and say, "Well, Eric, can you solve that?" Well, I do not know whether I can but I know that is -- even if I cannot it is not a reason to keep putting back into place something that did not work before.

DR. CHILDRESS: One criticism of the draft notes that we make the family a part of the health care team, that is care giving a part, but we then take the family away from this individual.

But let me just, before turning to Alex, raise one question for Zeke.

Your comments were stated in general terms. Do you take them to apply to what one might call procedural events, directives, as well as substantive ones, that is to ones that recommend a designated decision maker versus the advanced directives that set out standards for decision

making?

Your comments were just stated in general terms? You apply them equally to both?

DR. EMANUEL: As you know from my writing I think yes. I mean, I think the answer is if you look at substantive decisions we have lots of problems but clearly people do not feel about it. If you look even at procedural ones, appointing a proxy, you have a different set but also a set of -- first of all, people do not actually fill the documents out, number one. Two, when they fill them out they actually do not talk to someone so that you are sure that the attitudes are on the same wavelength.

Many of the -- I mean, a lot of this happens informally and people think what has happened informally is what happens formally.

If I could have a parenthesis because Eric prompted something which I think is extremely important and actually I think cuts across the report we heard this morning and this, which is our understanding of informed consent and what we really want to achieve. I mean, this is a process for something we want to achieve that is different.

I think Rhetaugh raised the issue.

If I could just for a minute say something. Informed consent occurs over a spectrum. The detailed elaborate delineation where you have really gone through it with someone and it is an extensive process and not just a form is an ideal.

DR. DUMAS: Right.

DR. EMANUEL: In both the settings that we are dealing with we cannot reach that ideal for many reasons it seems to me because we are asking prospectively way before the event and so we will not have a lot of the information.

We are going to have something less than the ideal and the question there for us is what are we satisfied with and what role is consent supposed to play in that process.

I think -- I mean, I am like Rhetaugh. We should never give up informed consent as a standard but we also should not fool ourselves that just because we have this piece of paper we have gotten informed consent and we have respected autonomy in that way. There are other things that need to be considered and I think -- I am just worried that again we may -- we may feel better but we actually have not improved the system and improved the protection and really respected autonomy any more by just having this form.

DR. CHILDRESS: After again Alex and Bernie, I am going to also ask Trish, who has been one of the major advocates for some kind of research advance directive in our subcommittee, to offer some views because we are hitting mainly the critical points and I want to get the positive ones.

Alex, and then Bernie, and then Trish.

MR. CAPRON: Zeke, I share many of the concerns about advance directives in end of life care that you have articulated. I do think it is worthwhile not being confused by the similarity of the phrase "advance directive" to import all of those problems to this area for several reasons.

Before I get to the reasons let me make one other preparatory comment, which is the problem always of the best being enemy of the good. I fully share with you and have spent years and years writing about the difference between the consent form and so forth and informed consent.

Our ideal ought to be an ongoing process of conversation between investigator and subject. Where that is not achieved the question is what do you do instead. Is it better to go ahead with an experiment that has no potential benefit to a mentally impaired subject who has never been asked whether or not if unable to give

contemporaneous consent he or she would want to be involved or is it better to go ahead where there has at least been the conversation and there was an apparent agreement to go ahead? That is the question.

I am not telling you that the answer is ineluctable but it does seem to me that if you -- it is possible to distinguish those two categories of subjects and I, for one, would think it is at least better, if not perfect because we do not know how good the consent process was, to go ahead where the subject has had it raised that there may be kinds of research that has no potential benefit to you. You do not have to participate in that. Some people choose to and some people do not. We are giving you an opportunity now to indicate your wish on that because at the point where it becomes relevant you may be in a phase of your illness where we cannot ask you or where you cannot answer us.

Now, I would argue that there is reason to believe that is preferable to going ahead when we have no -- we have never asked the question and we have never had that kind of directive.

Then the second question, when we face that issue someone is going to have to be involved in the decision process with the investigator. Do you have

someone whom you would be most comfortable playing that role? It might not be your mother or your father or your brother or your child. It might be someone else or it might be among those people, one particular one of them.

Again we might from the outside say that the choice of one of those people is not the best choice in the world and that there are psychological reasons why that person was chosen even though she or he is not the most informed or rational of all the people who could have been chosen. But again is there not something to be said with finding out what that person believes -- who he believes to be the person who is best able to step into the shoes and make a decision of the type that he would want to have made?

Now those are both things which you can achieve contemporaneously. The latter you do not really need but you might need it during like I am in surgery and I want my wife to be the one they come out and ask whether they should do something they were not anticipating. Fine. You can do that in the informed consent or you could do it in an advance directive.

With these patients that we are talking about here those same kinds of considerations arise.

It seems to me the fact that physicians caring

for patients at the end of life in half the cases do not even know that there is an advanced directive, that many people do not think about their own dying process and, therefore, do not fill out directives, that when the directives are written they are often written in terms that are too vague to apply.

Did he mean no food and fluids if we could get him over the hump here? Did he mean -- what is heroic methods? Those are not really very strong objections to the particular advanced directive for research that we are talking about here.

So I would hope that we would not throw out this concept simply because of a bad experience in another field and that we would not throw it out because it is not as good as the perfect ongoing process of discussion and fully informed consent going back and forth.

DR. CHILDRESS: Let me add one other point to that because I am not sure this came in Zeke's original statement. That is we are in this particular draft limiting this requirement to greater than minimal risk. That is very important because --

MR. CAPRON: Of no benefit.

DR. EMANUEL: No, no, no.

DR. CHILDRESS: It applies to greater than

minimal risk in nonpotentially beneficial research.

DR. EMANUEL: Wait a second. As I read the chart on page 150 it says --

DR. CASSELL: That is minimal risk.

DR. KRAMER: Where are you?

DR. EMANUEL: It says minimal risk.

MR. CAPRON: No, no, minimal has an X in it.

DR. CHILDRESS: The X is there. No, no, that is --

DR. EMANUEL: X means that is minimal risk, right?

DR. CASSELL: It just means the unknown.

MR. CAPRON: No, there is no -- we have not specified the requirements where it is minimal risk.

DR. CHILDRESS: That is right.

MR. CAPRON: Greater than minimal risk on people who are not going to get any benefit.

DR. CHILDRESS: See that is very important because --

MR. CAPRON: And we know this kind of research has gone on and we are disturbed by this type of research.

DR. CHILDRESS: And, see, that is a -- I am assuming that you are -- so I am assuming that you were building it into the -- would that lead you to state your

views differently now that we are clear about what we mean here because we are limiting this to greater than minimal risk nonpotentially beneficial research?

DR. EMANUEL: Well, I think there are two separate things. One -- sorry, I misinterpreted the chart. I apologize. I did not interpret --

MR. CAPRON: It is a fault of the chart. It is easy --

DR. CHILDRESS: Instead of X put --

DR. EMANUEL: It is my fault. I was -- I understand the -- let me separate it. I understand the motivation in this category of greater than minimal risk or no potential benefit to want higher levels of protections. I still object or still find the idea of trying to use advance directives -- not going to reach the objective.

What I heard from Alex and what I hear around the table is we share the concern. We need protections for people. The question is whether this answers that concern and whether this is the procedure that is going to answer that concern.

My sense, again importing some information from other areas, is it is not going to.

Two things in response to Alex. First, I agree end of life may not be a perfect analogy here. On the

other hand one should not be starry eyed, optimistic, as if there is no carry over. It is completely different because we have a lot of experience there and we have no empirical experience in this area.

Second, I am not sure I would pose the question as Alex did, which lets you -- I mean, the way Alex posed it was very stark. Either you talk to them and get their prospective consent or you do not and you just do it to them. Those are not the only kinds of protections. I would not -- I mean, if you ask me that question my reaction to the question is you have posed the wrong question. You have posed a false question.

DR. CASSELL: Could you elaborate on how? I mean, what is the alternative?

DR. EMANUEL: Well, I mean, it seems to me that if you have got --

DR. HOLTZMAN: He wants you to be closer to the mike.

DR. EMANUEL: I is coming.

(Laughter.)

DR. EMANUEL: I mean, first of all,

(Laughter.)

DR. HOLTZMAN: You better say the right thing.

(Laughter.)

DR. EMANUEL: First of all, I mean if -- here, I think, it crucially depends -- I think as Eric was trying tko suggest -- what kind of understanding of that research you have, whether it -- people who are concerned about this group that is going to be experimented on have been involved in the process of planning the experiments. I think those are other substantive protections that, in fact, lower my overall concern for the need to be sure you have got this full-blooded or as close to full-blooded consent as you have.

I think there is a trade off here in my own mind between the kinds of protections you have, how sure you are that there is no benefit to the subject, how sure you are that this is greater than minimal risk. Whether, in fact, the research results -- the community of concern thinks that the research results are going to be very important to them. These are lots of things that come into it and it is not just consent.

MR. CAPRON: But there certainly are needs for other protections. The question I think we have based upon experience that we have looked at in the psychiatric facilities is the willingness of researchers to (a) describe research or potential benefit that does not seem to be very likely to have any benefit but (b) the question

of where that trade off comes. And you can have had other people with similar illnesses agreeing and you can even have a legally authorized representative agreeing.

Our sense was you should not do something to somebody which has greater than minimal risk and by the design, even the designers would say, it is not designed to do them any benefit and any benefit would be totally adventitious and unexpected without that person having said if the time comes I am willing to be in that kind of an experiment because I, like you, Mr. Researcher, value the outcome of research enough to subject myself in a state in which I am not capable of protecting myself and not capable of indicating that I want to withdraw, and everything else we think of as normal protections that people have I, myself, am willing to take that risk in order to advance science.

It is here, unlike -- I mean, I do not know what I feel in the end about all the losses that will -- if we cannot get access to every human tissue without consent -- I mean, you know, I do not know where I come out on that yet. You all will still have to convince me. But I do know what I think about living human beings who cannot protect themselves and are going to be used in greater than minimal research. I do not want it done unless they have

said it is okay with them. That is just the bottom line on this point.

DR. CHILDRESS: Before I turn to Bernie, Trish and Eric, let me just note Harold and Eric Meslin had called my attention to what appears to be an error on 145 under four, "and IRB may approve this category of research only if the potential subject has given informed consent." I think the "and" should be "or." Has actually given advance directive to be consistent with --

MR. CAPRON: It says "or." "Or if incapable has executed an advanced directive," doesn't it?

DR. CHILDRESS: On 145?

MR. CAPRON: 145, second line --

DR. MESLIN: Second line of four.

DR. CHILDRESS: Mine does not.

MR. CAPRON: Oh, no. Look at the top of the page.

DR. CHILDRESS: I know but --

MR. CAPRON: Oh. Oh, I am sorry. I was looking at the top of the page.

DR. CHILDRESS: Look down under number 4.

DR. SHAPIRO: Could you read that again?

MR. CAPRON That is potentially beneficial.

DR. CHILDRESS: That is right. We do not

require --

MR. CAPRON: Three --

DR. CHILDRESS: -- an advance directive for potentially beneficial.

MR. CAPRON: That is right.

DR. CHILDRESS: But it says it under number four. At least our draft says it.

MR. CAPRON: Oh, I am sorry. I am sorry. I understand.

DR. SHAPIRO: Can you repeat that?

DR. CHILDRESS: Yes. It should be -- the "and" should be "or."

MR. CAPRON: The thing that we have been discussing is point number three and you are now switching to point number four.

DR. CHILDRESS: Well, this is just to get this clarification in. Thanks to Harold and Eric for calling it to my attention.

Bernie?

DR. LO: Yes. Let me also speak as someone who has tried to work in the field of advance directives and end of life care and it has been disappointing to say the least that it has not worked out better. So although I think we cannot translate all that experience, there

actually are some pertinent differences, and one being, I think, that some of the people you are talking about as potential subjects may have a remitting and relapsing course -- I mean, there are moments of whatever you want to call it, remission or treatment -- may be able to be quite decisionally capable and actually have some sense of what it was like to relapse.

But I am very skeptical about many people filling these out. I mean, some will. I guess you want to give that opportunity. But I guess my suggestion would be that what you are really doing, I think, with the current proposal is saying for all intents and purposes research that does not provide benefit and is more than minimal risk is probably not going to happen. It is going to -- you are going to have to work very, very hard to find that small group of individuals who are willing to fill out that research advance directive and you probably will not. That may be fine if that is what you want to do.

I have some other comments that have to do with sort of our conceptual thinking behind why we -- why are we so willing to say that a piece of paper which is really just a signature and a notarization and may not express any more understanding, commitment or having thought through a decision, I think it really goes back to this notion of

informed consent. I would like to suggest that informed consent is important but we should not try and make things sound as if they are very much like informed consent when they are not.

I think the real issue is that it is not that we get consent or not, that we do not want to do things to people that they would not want us to do or they did not even know about and it is just very uncomfortable. If they consent we figure, well, they let us do it so that is okay. But I think there are other degrees of respecting autonomy, many of which I think you have worked into the report.

One is failure to assent even if the patient is uninformed has to be respected. I think that is very important and I would say that you actually have to seek affirmative assent. You cannot just say they did not object so we will do it. You have to say is it okay if I draw your blood.

I think that is -- you know, we were talking about incremental improvements this morning. I think that is an incremental but substantial improvement over what happens now where you just get the blood drawn because, you know, we want to draw your blood and you do not object.

I think the other thing we tend to do is we try to fit everything in some autonomy model even when it does

not. Most of these decisions for people of questionable capacity really have a lot more to do with what someone else thinks is in their best interest.

I think one of the things that I like about this draft that I think we need to sharpen even more is a willingness to say that family members by default, unless shown otherwise, are the natural surrogates to whom we turn for decisions about is it in this patient's best interest to be a research subject. That is a big change. I mean, if we are willing to say that leaving aside the -- it depends on whether it is benefit and risk.

But, you know, Alex, to go back to what you always reminded us sort of the history of this. I mean, there is a school of thought that, you know, it was very, you know, cogent, I think, that said, no, that you cannot do anything to a subject without their free and voluntary consent. It goes right back to the Nuremberg code. So that if we are really saying a family member may consent or may give permission under certain circumstances, again that is -- and if we really involve the family members in a meaningful decision as best they can make it, again I think that is an incremental but substantial improvement.

As long as I have the floor I am going to just sort of sneak in another point that is unrelated.

I was impressed that a lot of the recommendations are let's have the good people in the IRB settle this one for us at the local level.

(Laughter.)

I guess I am really skeptical. I mean, it may be --

(Simultaneous discussion.)

DR. LO: Should we do a global search and replace? This is a really tough question. We do not really have a good answer yet on how to solve it. We are still thinking but in the meanwhile we are going to pass it on and we hope these poor overworked, under trained, unpaid people in the IRB will do a better job than nothing at all. But I think we really should be fairly honest and say if we are saying the IRB should decide on a case by case basis and recommend, that is really not a very robust guarantee.

DR. DUMAS: I agree.

DR. CHILDRESS: Trish, and Eric, and I think I saw David's hand.

Trish?

MS. BACKLAR: First of all, I want to say that it is a shape --

DR. SHAPIRO: The microphone.

MS. BACKLAR: First of all, I would like to say

that it is a shame that we are calling this an advance directive because I think that it is a very -- the document that we describe as a RAD in here is really very different from the kind of advance directive for end of life care.

Secondly, I see it much more as a kind of ongoing contract with the researchers which can change as time goes along so if the subject objects at any time they can go out. Plus it involves certain safeguards like a surrogate decision maker. Plus I do not know if we actually filled this out -- I have to go back and look and see exactly what Jonathan said.

But there should be also some kind of outside health care provider who is also involved and is not part of the research so that it is not simply an agreement to be in a research protocol and it certainly should not be done ahead of being -- I mean, it should be part of the informed consent process. The surrogate would be part of the informed consent process. All the safeguards would be built into a contract to protect the person who may have fluctuating incapacity.

DR. CHILDRESS: Have you taken out -- I guess one question would be then what role advance plays in this at all?

DR. CASSELL: What role has what?

DR. CHILDRESS: What role advance plays in this? I mean, this is just before the research but it is hardly advance in the same sense that we are talking about so maybe we have the wrong language here.

MS. BACKLAR: Correct. Maybe -- because since you notice in the RAD it really has to be tied to a specific research protocol. It is not just for any research that may come along.

DR. CHILDRESS: But then that is -- then perhaps we are misleading.

MS. BACKLAR: Right.

DR. CHILDRESS: The report needs to be altered then and basically get rid of the language about research advance directive.

DR. EMANUEL: Could you just tell me -- say I have a waxing and waning condition. I do not know. Manic depressive disorder or something.

MS. BACKLAR: Right.

DR. EMANUEL: How exactly -- and the researcher wants --

MS. BACKLAR: The research --

DR. EMANUEL: -- the researcher wants to get me at the depressive moment. Okay. That is whatever the research is. It has got to get me at that moment. Now how

is it going to do it? I mean, basically what you have described is informed consent. I do not see how it is anything different than informed consent. An advance directive --

MS. BACKLAR: I tell you what is advance about it.

DR. CHILDRESS: It may be an improvement --

MS. BACKLAR: The advance part of it is in a sense the person is preparing in case they lose capacity and at a time that they lose -- they should lose capacity for decision making if they are in the research protocol, which might involve coming off medications or various things, that for sure they have with them a surrogate and an outside provider. So in a sense that is the advance part of it.

While they have capacity to make decisions for themselves they will.

DR. CHILDRESS: But we could simply require those mechanisms without connecting it with the notion of an advance directive.

DR. EMANUEL: I also might mention that does not apply well to the dementia category, which at least from a numerical standpoint --

MS. BACKLAR: I understand that.

DR. EMANUEL: -- is a much bigger category.

MS. BACKLAR: Well, we -- what I was thinking of is setting up a model out of which one might change in terms of the different categories. You will notice in the beginning we categorize people with capacity. We have four kind of models. This was really set up thinking of people with fluctuating incapacity.

DR. CHILDRESS: Anything else at this point, Trish?

MS. BACKLAR: Not at the moment.

DR. CHILDRESS: Okay.

Eric?

DR. CASSELL: Well, it is King Solomon's headache revisited.

(Laughter.)

Bernie is absolutely right about a very crucial issue. Here it is we want to move forward, the decisionally impaired problem is here, we have got to solve it, and then we come right up against it and we are going to use the same mechanism that did not work before, and we are going to use the same IRB. Bernie and I are jumping up and down and saying, "education, education, here, there and everywhere," but we are not educating them. We are going to go in there and talk about an advance directive and we

cannot even agree on what that is.

And then even here in number four where an "and" is being added -- gee, that -- wait a minute. That means that --

DR. CHILDRESS: No, the "or" replaces an "and."

DR. MESLIN: It is being replaced.

DR. CASSELL: The "and" replaces the "or," right?

DR. CHILDRESS: No, the "or" replaces "and."

MS. BACKLAR: "Or" replaces the "and."

DR. CASSELL: Oh, thank God for that. That is okay.

(Laughter.)

DR. LO: We solved that problem.

DR. CASSELL: So that is solved.

Now all we have to do is solve the problem of we do not know what an advance directive is and we are depending on an IRB.

I do not want to go back and say, "Well, that is it. We gave it a run and we are not going to do it." The Edsel was not a good car and that is all there was to it.

MS. BACKLAR: And we still have not agreed about risk.

DR. CASSELL: So then the question is what is the intermediate solution. Is there an intermediate solution? Well, there is a research solution to it, among other things, where we strongly urge the National Institutes of Mental Health to put out an RFP on researching the issue and we request them to come back to us with this saying we cannot resolve this issue because there are too many questions of fact that have not been solved for us. Otherwise we are just writing a bunch of stuff that we know as we write it does not work. I do not want to do that.

I do not want to come back and say, "Well, it does not work but we are going to write it down anyway," or end up with a good workable report where all the way through the body of the report it is a great report and then we get to the conclusions on which policy is based and we are back where we were.

DR. CHILDRESS: David, do you have anything to add to that sobering thought?

DR. COX: Yes, with some trepidation actually.

So this is an area where I have very little personal experience but I have found listening to the discussion it leads me to the following questions:

I am very keen on, you know, not instituting

things that knowledgeable people who have personal experience say has not worked. But I ask the question why hasn't it worked?

So that I can think of two reasons why it might not have worked. First, that there is sort of factual practical things that makes it not practical. And another thing that I think is more likely why it does not work is because people do not value the principle on which it was based to begin with.

Now if people do not value the principle that it was based to begin with we can have any process that we want to put together and that will not work either.

So because it strikes me -- again, being naive in this area and I say that -- that this should not be so complicated. All right. So when things smell like they should not be real complicated and are real complicated it heads me towards the fact that some people do not value it.

So I really very much like the idea of going back because there is lots of experience in this in asking why it did not work, okay, and what we have to do to get fixed to get it to work. And that the -- rather than making another set of recommendations sort of addressing that fact right up front. And then, okay, if it is not valued by certain people have them come out of the closet

and so on, all right.

Or if they say it is not that we do not value it but that it conflicts with some other value that we have that precludes us doing it.

Now, again, I say that I do not have any background in this area and maybe this is not relevant but just listening to the discussion --

DR. CHILDRESS: Let me add one point before getting to Eric and Bernie.

When we ask the question would it work here, has it worked in another area, I think we do have to ask work in relation to what. The critical question here, and I think we saw it in the exchange between Zeke and Alex is work in terms of facilitating research, work in terms of protecting subjects and their autonomy.

I am not putting those in cast but work -- it was differently -- there was a different emphasis in your comments as to whether it would work or not I think and it seems to me that the fundamental attention that we have to face in this area because it can -- it can certainly be said it works if only one percent fill out a form it works in one sense but it will not permit research to go forward. So a lot depends on what you are emphasizing, I think, in terms of what works.

DR. EMANUEL: Wait a second.

(Simultaneous discussion.)

DR. EMANUEL: I am a little uncomfortable here by people saying that if we have the form filled out that is the only way in which we have protection of --

(Simultaneous discussion.)

DR. CASSELL: No, it falls on the straw man.

MS. BACKLAR: It has nothing to do with just filling it out.

DR. EMANUEL: As an integral, essential, inescapable part.

DR. CHILDRESS: It is a sorting device.

DR. EMANUEL: No. I am hearing if you do not have this consent you are out. You are not protected. We have no assurance of protection and you are out.

DR. CHILDRESS: No, we did not say that.

Alex, explain it.

MR. CAPRON: Well, if you do not have this -- if you -- put it this way: We would have many more advance directives for end of life care if the public and physicians knew that every medical technology had to be used on every patient who did not fill out an advance directive, which I would regard -- most of the care that would be provided beyond a certain point would not be

beneficial to those patients. It would be in the same category as this. People and doctors, if they knew they had to labor over every patient until physiologically they had total collapse of the patient, and unless there had been an advance directive we would have a lot more advance directives.

I have a sense that if researchers believe that their IRB's will not allow them to do research of a certain category unless they have discussed that category of research with the subject in advance at a time when the subject can make a choice, and as you and Bernie have pointed out this is much more applicable to people who go in and out of periods than to someone who is on a course because the person who goes in and out has some sense of what you are talking about. The person with Alzheimer's -- it is a harder prospect to know.

But the incentive will be there to have those conversations and to have that sorting.

Now once you get a person who is in the category that they, themselves, have said it is all right it is not as though you have carte blanche with them of course. But the understanding is that no research institution will allow the research to go on at a greater minimal risk of no potential benefit on those people for

whom that -- I prefer to think of it as prospective consent instead of an advance directive. Prospective consent and appointment of their surrogate.

They have not gone through that process or they went through it and they said no, they were not interested, or whatever reason. If you do not have that from them they are out. They are protected in a sense that they will not be subjected to that except by someone who is willing to break the law.

DR. CASSELL: I want to see examples of the advance -- I mean, the advance consent, which I think is a good distinction.

DR. CHILDRESS: I am sorry, Eric. I missed that.

DR. CASSELL: I would like to see copies of what you mean. I mean, you can write a general, very general statement of somebody approves the research, they really would like to be a member of a research project even if they cannot consent at that time, very general statement and then I understand what the person is doing but the more concrete you get the less valuable the thing is and the more broad it becomes the more question there is are they really consenting to the --

MR. CAPRON: And the key thing that you are

trying to distinguish as I have understood what we were about here is whether or not you would agree to be in a consent protect that would expose you to greater than minimal risk and that has to be explained with the kind of things that could happen and make it concrete but would not be designed to benefit you at all.

And that is the determination that is so crucial here because that kind of research is done by researchers and it should only be done when the person has said, as the researcher is saying, I value scientific knowledge enough to go through a process with no prospect of being benefitted by it as opposed to with the lure of some potential therapeutic payoff for me. And that is why we distinguished it. We do allow a surrogate in the potentially therapeutic because we say there the fact that you have not gone through this process and have not made that determination ought not to be a total barrier to your getting that benefit of the innovative treatment or whatever is being done here.

But where that is not a prospect what is the justification for using the person? It is just pure use of a person who has not been given the opportunity to say yea or nay to that. Not everybody can be presumed to be willing to go through pain and suffering in order to

advance science.

DR. DUMAS: Yes, right, very true. I do not understand why --

DR. SHAPIRO: Microphone.

DR. DUMAS: I do not understand why it is so difficult. You know, I sit here and I think these things seem to be in general -- they are addressing problems that we talked about a long time and they seem solvable. I do not understand why it is so complicated. I have a feeling that it is not really that complicated. Why are we doing this? What is going on? What is going on?

DR. CASSELL: It is complicated. Rhetaugh, it is complicated because we are trying to say we want to find out what this person would think to be in their best interest as they know those interests.

DR. CHILDRESS: This is not the --

DR. DUMAS: Well, you do not ask that question.

(Simultaneous discussion.)

DR. CHILDRESS: That is the case here.

DR. DUMAS: No. You ask that person -- you tell that person something about the research you are doing. You ask them if they are willing to participate. You explain as best you can what the implications are and you extract a yes or a no, or I cannot answer, or something

like that. I just do not -- I do not know where we are in here. I know there is some underlying issue here that is not on the table.

(Simultaneous discussion.)

DR. CASSELL: The requirement could be for a drug company, Rhetaugh.

DR. CHILDRESS: It may be that our chart is not as clear as it should be because, Eric, I am not sure how you would say in terms of non potentially beneficial research with greater than minimal risk that this is a best interest consideration. I mean, how could --

DR. CASSELL: Well, it is like the people who participate in Phase I trials.

DR. CHILDRESS: They may want to but how do we say do it as a best interest consideration?

DR. CASSELL: Well, because the person thinks that in most instances that some good should come of all this.

DR. CHILDRESS: That is true for those who consent but I do not think you want to say that to the person who does not have the capacity to consent and that is the category we are talking about.

MR. CAPRON: Eric, it does not fall within the usual understanding of best interest. It seems to me that

a person can make a statement that they have interests other than their physical well-being and you could say that is part of their best interest. But usually when we talk about best interest and about people who are incapable of deciding we are talking about something more immediate.

It seems to me that the person who has a dread disease and says you want to do a study unconnected from my disease or connected but of no benefit to me and I am willing to participate is saying I am trading off in a larger existential sense my own personal benefit for some greater good and I am trying to give some meaning to my life right now that I am still a person capable of doing something useful for others even though I have this dread disease.

DR. CASSELL: Well, I --

DR. CHILDRESS: But that is not --

MR. CAPRON: And you can say --

DR. CASSELL: Well, let's back off back to the other issue.

MR. CAPRON: But the --

DR. CASSELL: Supposing there is no problem about that and I agree with all of it and then back off to the other category. We have no problem except that one? Is that our only problem?

DR. CHILDRESS: That appears to be the case actually.

DR. DUMAS: I think it is immoral to persuade somebody to participate in a project that you know is not going to do them any good and that has more than minimal risk.

DR. CHILDRESS: Larry has been trying to get in and he has not spoken. Let me get him and then Bernie and then Trish.

DR. MIIKE: Am I close enough? I guess I am.

What is the universe we are talking about here because elsewhere in the report you say that if your research can be done in other subjects then they are not to be done in the decisionally impaired? So what we are talking about is an area of research in decisionally impaired subjects where there would be greater than minimal harm. What kinds of research are we talking about that would still escape the prohibition about if it can be done in other groups?

DR. CHILDRESS: Bernie, did you want to respond to that?

DR. LO: Yes. I mean, I think there is a couple of things we -- we sort of jumped in the middle of the end of the report and there is a beginning of the

report I think we need to set up. First there is a long-term benefit to people with things like -- with conditions such as depression, dementia, to have research done that does not give them direct benefit but illuminates the condition they have, the etiology, things like that.

The problem is that some of the things which are not very risky to people who have decision making capacity can be quite risky in some sense to people who do not so that is things like CAT scans, MRI scans, PET scans, which for people who are aware present most of the time very little risk. To someone who does not understand what is going on it can be very frightening. One might, depending on how you construe greater than minimal risk, might say that.

What is missing out of, you know, the way this has fallen out is the notion that was there before that has been in previous writings on the subject that it makes a difference whether the research is pertinent to the condition that the patient has or not.

Now one thing you have done, which I have not thought through yet, is when you say that it makes a difference whether you could do the research on subjects who are able to give consent or not. But, I mean, if you want to study, for example, what the glucose metabolism is

in people with severe depression that is refractory to other medications because you want to see if a different area of the brain is involved because that might eventually lead to new drugs but it is not going to benefit that particular patient and the test, which is getting a fancy x-ray, may scare them.

It is hard for me to imagine how you do that research if you say it is only going to be on people who have given a research advance directive or whatever you call it. Realistically we are not going to do that research. If we are willing to say that we do not care, we are not going to do that research and accept the downstream consequences that is okay. But I think to say that, you know, we can make this -- I mean, I would like to believe we can make it happen because we are going to be committed, we are going to realize it is important and we are going to mobilize the activists, I am not sure it is going to happen.

MR. CAPRON: Would you be of the view that Eric expressed that the statement you have just made is an empirical statement that ought to at least be studied before we reach the conclusion negative to the use of the directives? In other words, if you are saying that this is a requirement which is a veiled way of stopping all

research not of benefit, that is a disturbing claim. I am not convinced of it.

DR. EMANUEL: I think that has to be the presumption, Alex, given the history and the burden -- I agree with you. We need to have empirical studies. It is an issue of fact. It is an issue of fact but the history of the use of advance directives has to suggest to you that it is unlikely and that the burden of proof is, you know, quite --

MR. CAPRON: I mean, because in most states you do not need an advance directive to get appropriate end of life care and if you do not get appropriate end of life care it is for reasons other than the fact that you do not have an advance directive.

DR. LO: Alex, wait. New York is a state and Missouri is a state where that is -- legally you need an advance directive to get life sustaining treatment withheld or withdrawn generally.

MR. CAPRON: No, you do not. You need clear and convincing evidence of your views which does not include an advance directive.

DR. LO: Okay. But most people do not --

(Simultaneous discussion.)

DR. LO: Most people --

(Simultaneous discussion.)

DR. LO: Well, the law requires clear and convincing evidence. Most people do not give it. What happens in New York is that doctors want the law because it is the most ethical thing to do.

MR. CAPRON: Right. That is my point. That is why you could say that "advance directives" have been a failure and why everybody in the country does not have one because the message is out there to people and their doctors that these decisions are going to get made anyway.

As I say to you, do a thought experiment, if the experiment I described before was the case where everybody got the full court press everything medicine could do until they fell apart biologically or physiologically you could be damn sure that there would be a lot more people having advance directives and every doctor would raise it with any patient who he thought was within ten years of death because he would not want to be stuck having to do that.

DR. EMANUEL: Alex --

MR. CAPRON: But that is not the case. That is why advance directives have not worked here. We all avoid thinking about death, et cetera, et cetera, et cetera. That is not the case with these patients if they are in

contact with a researcher. The researchers say to themselves I can only recruit this patient if I have had this discussion. If I have said, "Are you willing to go into such an experiment, an experiment that would not be for your own benefit, and that might cause you more risk because you --" all the kinds of reasons that you have given, "-- or are you not?"

DR. EMANUEL: Alex, is that the right model? Is it the model that I have a stable of patients with manic depressive disorder and I have experiments waiting to bring them in or does the situation actually work in a different way, which is I come up with an idea for a study because of, you know, whatever is going on in the literature and then I look for the patients that are going to fit the study. If it is that second model you have a problem and you have a problem --

MR. CAPRON: You have to --

(Simultaneous discussion.)

MR. CAPRON: -- to their physician to give the consent.

DR. EMANUEL: Wait a second. You have a problem because the idea of an ongoing relationship between researcher and subject that you suggest where this is going to be prospective consent is not operative. It simply is

not going to work. So then we are going to step back -- these research advance directives are going to be general things not made with the specific researcher who is going to do your experiment at all and they are going to become, you know, some kind of carte blanche.

DR. CASSELL: Mr. Chairman, could I ask for clarification?

DR. DUMAS: Wrong, no. No.

MR. CAPRON: Wrong.

DR. CASSELL: I just want to clarify the question we are discussing.

DR. CHILDRESS: Use the microphone.

DR. CASSELL: I take it that we have made a change in therapeutic research even where risk is present, that the family, for example, or a representative can now consent whereas before that was not the case, I mean, in previous lifetimes that was not the case. We put that in. We have added the family or legally appointed representative. Now we are arguing only about one area, nontherapeutic risky research. That is the only thing we are discussing.

DR. CHILDRESS: Greater than minimal risk, nonpotentially beneficial research.

DR. CASSELL: Right. But we have as a

commission come to believe that we can protect our subjects by having their family or equivalent there in other circumstances where it is therapeutic and there is risk. So now we are only about nontherapeutic risky experiments with minimal risk. Is that the question?

DR. CHILDRESS: That is what I understand this to be.

DR. CASSELL: If that is the case and we are going back and forth, we are discussing a matter of fact, a question of fact. If that is the question then from my point of view it ought to be left impossible to resolve and we ought to set in motion something that will help resolve it where that is really clarified so that we can find out this question. Otherwise we are just guessing. You are saying yes and he says no.

(Simultaneous discussion.)

DR. EMANUEL: No, no, I am not --

DR. CASSELL: He says yes and you say no.

MR. EMANUEL: I do not think it is just a matter of fact because as I have heard the discussion for one second, Alex is prepared to say even if my prediction or Bernie's prediction or anyone else's prediction that you will not get people to fill out advance directives, that the system will not work, he is prepared to say fine, it

will not work. But I am not prepared to change the standards. He does not care what the facts are, right?

(Simultaneous discussion.)

DR. CHILDRESS: But again our work has to do with values not simply with --

MR. CAPRON: That is right.

DR. EMANUEL: No, no, no, will not work in the following sense. People will not fill out advance directives and the researcher --

(Simultaneous discussion.)

DR. CHILDRESS: It works from Alex's standpoint.

MR. CAPRON: It works. It prevents research on unconsenting subjects that exposes them to more than minimal risk and no benefit. It works.

DR. CHILDRESS: It works.

MS. BACKLAR: I think, Zeke, you are talking about something quite different. First of all, I do not really see an analogy to end of life advance directives. That is because if you make out an advance directive about what will happen to you when you die you do not know what that is going to be. You have no way of knowing right now how your end of life is going to be. So it is always conjecture and there is always going to be some kind of

reluctance to make out something of which you know nothing.

This we are talking about something like a psychiatric advance directive. You may not have had precise experience but you should have had some experience perhaps in losing capacity to make decisions for yourself. All you are doing is with a specific protocol putting in place certain protections for yourself should you lose capacity during that research process. And that will be those protections of a surrogate and an outside health care provider.

DR. CHILDRESS: But I just might note we can put --

MS. BACKLAR: And the ability to drop out whatever happens. If you object you get out of it.

DR. CHILDRESS: But see this is why I think, Trish, as you and I have discussed several times, it is really important to distinguish the notion of advance directive from all these other protections and as long as you can inflate them then a lot of this debate is going to go on.

MS. BACKLAR: Okay. I am willing --

DR. CHILDRESS: We could require these protections --

MS. BACKLAR: -- the reason --

DR. CHILDRESS: -- whether we have advance directive or not.

MS. BACKLAR: The reason that I see --

DR. CHILDRESS: Right.

MS. BACKLAR: -- this kind of contract as a good thing in the partnership between the researcher and the subject is that it is a way of getting those protections all into a package. That is all. And that the surrogate is there and part of that consent process, understanding what is going on, plus the outside provider, that is it. Just a sort of package to ensure protection.

DR. CHILDRESS: But in our study we have a lot of contracts that are regulated in various ways and we could simply require these components you have mentioned and that would be separate from the question of whether you have to have an advance directive before you enter it.

MS. BACKLAR: Right.

DR. CHILDRESS: That is -- I think we have to keep those separate. If we do not clarify those in the report we will be going around and around on this.

But Steve wants to get in.

DR. HOLTZMAN: Again I am not terribly familiar with the area but it will not stop me from talking.

If I understand what you are doing here, when

there is potential therapeutic benefit, even if there is greater than minimal risk, you are saying that a third party who cares about the individual can do a cost benefit analysis and make certain assumptions about that individual that they would have certain values involving benefit to themselves and risks. Whereas you are saying it is not legitimate for a third party to make that kind of cost benefit analysis where the benefit are not benefits specifically to the individual. It seems to me that is the bottom line.

The question I have -- you are talking about an empirical study of whether or not there would be enough subjects for that kind of research. The question I would have is are there significant classes of disease in which it is in the nature of the disease that the individual will never be in a position to be able to give such an advance directive?

If that is the case and if there is valuable research, which is in its nature is not beneficial to the individual but to understanding the disease, hence directly to the individual, and involves potential harm or less than minimal risk and that is understood as Bernie has said it, where it might be not risky to me but risky in another sense, right, then effectively this is saying that research

will not be undertaken.

If I understand Alex, Alex's position is that is the morally right thing. That research ought not be undertaken. Okay.

So I am not sure that it so much an empirical question about whether the advance directives -- that is a question of how much of that kind of research we are going to forego.

DR. EMANUEL: Can I clarify the empirical question? I think that is a good point and here is the empirical question: If we survey these people and they said -- when they are competent and they said, "Yes, I would like to participate in research," and then they did not fill out an advance directive. That would show that advance directives, in fact, did not work in exactly the way Alex wants them to work, which is a true expression of person's preferences. Is that right? That is the study we need. That data actually is a relevant piece of data. Separating preference from action here.

DR. LO: Let me just quickly respond to Steve's comment are there classes of patients who would never be able to complete this prospective consent. It seems to me people who never had decision capacity -- so people born with severe developmental disorders who never have the

capacity to make an informed decision. It seems to me those people would be excluded from this class of research. My point would be they would also, therefore, be cut off from any benefits that might flow from this greater than minimal risk, not beneficial to that individual research, because you will not understand some basic things about the causes of the epidemiology and causes of illness.

DR. FLYNN: Can I just speak to this because I do have a lot of concern that we are not aware of what this research really is. There is a huge set of investigations going on now that look at the basic biological processes that underlie severe mental disorders. Most people who are involved in that research I think are capable of and do, indeed, participate in giving their informed consent.

But those who are potentially the most important to study, those who have almost no remission of their symptoms, those who are multiply impaired, those who have had virtually no way to give their advance consent or participate in a process are some of the folks whose participation is most crucial to understanding and being able over time to ameliorate and ultimately conquer these disorders.

It is important that we build protections for these folks. It is completely unacceptable to me that we

would set up in place a standard that would essentially stop such research if there were -- if that is where we think we are going. I do not think we want to do that. I think we want to look at feasible and useful ways of creating a participation for those subjects that assures the research goes forward because it is crucial and at the same time protects them.

I think that is what Trish was trying to bring to us in looking at as one tool the research advance directive. But we certainly do -- and I was very troubled to see that families were removed from that potential role with some of these populations.

But I do not want to have the conversation continued with some assumption that we are willing to give up this research because we cannot seem to find a way to adequately protect subjects and yet let this important research go forward. Remember greater than minimal risk is not necessarily extraordinarily risky sets of experiments.

DR. CHILDRESS: It seems to me that this is one place, let me get some feedback, where we could profit a great deal from some input from investigators and others over the next few weeks and I am not necessarily talking about a study but get some feedback on this. One of the -- as you recall from the discussion with the Genetics

Subcommittee this morning, the possibility of putting out -- we are not ready for that yet because we need to get recommendations further along, but putting out a draft report and getting feedback.

In part of that I think we do need to get feedback on this from people who work in the field, including the kinds of comments that Laurie has offered. That is one thing I think would be very useful for us. If there is agreement we will work out some way to do that.

Alex?

MR. CAPRON: I think we have heard enough that before that report goes out we have got to go back to the drawing board to a certain extent because like the Tissues Committee we simplified and Larry was urging simplification before, and no more than so many categories, but we may have gone beyond Einstein's dictum that we should make things as simple as possible and no simpler.

Because the desire not to distinguish between more than minimal risk and things which impose severe pain or threaten life or function, bodily functions, and the different -- the failure to differentiate between those of permanent loss of decision making capacity when our real focus in this has been those who have some diminished but often fluctuating and often varied capacities, the capacity

to decide some things and not others.

And our failure to distinguish between institutionalized and non-institutionalized individuals may have led us to reach conclusions where I would be certainly open to the notion that there can be a definition of the benefit of -- prospective benefit to a group of people of whom the individual is one. Where if you had some -- both extraordinary proof that there was no other way of getting this information rather than just as an avenue of convenience, indication of the great value of the information and some surrogate process beyond the individual's relatives because we know that there are many relatives who are very protective.

We also know that for some long-term institutionalized people there are relatives who have relatively little attachment to the individual and who are not really likely to exercise the kind of concern that we are expecting from them.

This may just be a topic where the devil is in the details and we have got to go back and attend to those details a little bit more and we do not want to paint with too broad a brush. I continue to think we should go into it with a very strong presumption that the efforts should be addressed towards getting people to seek that consent

and to go through a process of finding subjects at times when they are able to consent, Zeke, and working with people longitudinally instead of just saying, "Gee, I need subjects and I want them to be depressed and so I will get them when they are depressed right now rather than having to take the greater effort to work with them over time until they come to a point where they are not depressed and can anticipate a future episode and how they would be willing to react at that time."

DR. CHILDRESS: So this is kind of conceptual normative work to be done?

MR. CAPRON: I think it is -- yes, conceptual normative.

DR. CHILDRESS: What else do we need to do?

MS. BACKLAR: Perhaps we actually need to do some boxes. God help us.

DR. CHILDRESS: These are not boxed boxes but they serve the same purpose but we may need more complicated one along the lines of Zeke's several categories. We will influence Jonathan soon enough.

MR. CAPRON: Jim, there is another generic question that -- usually I do not think it makes sense to spend a lot of time as a whole group wordsmithing, but I have been bothered with the draft as it now stands by the

term that we have used, the adjective we have used to describe decision making capacity, which is questionable. And we are searching around. At other times we say decision making capacity is in doubt.

There is something about -- and if other people do not share my sense I will simply -- I mean, it is not something I feel strongly about. It is just it bothers me. The word "questionable" is usually used in context where you are making an adverse judgment about the person involved. I mean, he is --

DR. _____: Questionable character.

MR. CAPRON: A person of questionable character. A painting of questionable authenticity. I mean, et cetera, et cetera.

I know it does not mean to attach to the individual but in a way it rubs off a little bit. If anybody creatively could suggest how we -- without saying a person who may lack decision making capacity or whose decision making capacity may fluctuate or whatever -- even uncertain it strikes me is a better word than questionable. But, I mean, I have made the point and --

DR. CHILDRESS: I think that is --

MR. CAPRON: -- this is more or less something to submit to you and Jonathan if people have some

creativity.

DR. CHILDRESS: And Diane was -- because a part of this grew out of our discussion in early December at the conference which used this particular title and part of it is an effort to get at how the subject is first sort of confronted. What do we see? Questions are raised about the person's capacity to consent.

However, your point is well taken.

Diane, do you want to respond?

DR. SCOTT-JONES: We did spend a lot of time discussing this issue, Alex, and I agree with you. It is not really an elegant or a precise term to use but if you use other terms such as uncertain, uncertain connotes lacking self-confidence or something like that so it is not the best term either. What we were using before, decisionally impaired, became awkward in its use throughout the text.

I think part of the problem is that we are lumping together and calling a population be referred to persons who lack decision making capacity as a population when, in fact, there are many different groups who are being lumped under this rubric and a better choice -- I do not think we can practically do it but a better choice would be to talk about persons with various disorders

separately and call them by some more descriptive term. I think we are going to have this problem as long as we are lumping together disparate groups of people and that is where the problem lies.

DR. CHILDRESS: But we are interested, in part, in what they share and it is how we described what level used for what they share that becomes critical for the report.

DR. SCOTT-JAMES: But what they share is not really always shared because some of the persons covered under this chapter would be incapacitated almost all the time. Some others would be rarely incapacitated. We even put children in here and we tried to fix that a bit by referring to younger children but we even put children in here who are developmentally appropriate in their decision making. So it is just --

MR. CAPRON: That is one of the reasons we dropped impairment.

DR. SCOTT-JONES: Right.

DR. CHILDRESS: Zeke -- oh, sorry, I missed the comment.

MR. CAPRON: Well, that is one of the reasons we dropped impairment because a child of seven who does not have an adult's decision making capacity is not impaired,

it is a normal child, but they do not have full decision making capacity.

In some ways the question that Laurie was raising before about people who are born with disorders which make them always unable to participate in decisions are not even covered by this report as it is now entitled. They are not of questionable decision making capacity. They lack decision making capacity.

I mean one escape is to say this report narrowly addresses the category of people who go in and out of decision making capacity and where you have to make certain in any circumstance where they are when you are engaging them in the consent process.

DR. CHILDRESS: Zeke has a creative solution.

DR. EMANUEL: No, no, no. I am struck as I was struck actually this morning by the fact that we seem to all be in the grip of a different kind of picture as to who these -- fit into each of these boxes.

It may be that what is in your mind, Alex, is a certain kind of experiment that really stuck out -- stuck with you and I may have a different kind of experiment as the sort of paradigm that I am thinking these rules ought to apply to. Part of the reasons we are at loggerheads is because we have not made these distinctions.

I think Laurie hinted at some of the kinds of distinctions we should make. I think -- and this, I think, applies equally to this morning's session -- it might be helpful if we had some paradogmatic cases to see if we could agree on them and understand them. You know, are we talking about sending someone into the PET scanner with an A-Line is? Is that the kind of case that we are really talking about as greater than minimal risk with no potential benefit for them? Or is it something else? A more invasive procedure than just an A-line but we are talking about a -- you know, I do not know -- bronchial or, you know, something else?

So I find this -- we are talking in the abstract sometimes and I think having some cases might be helpful.

The second thing I would like to raise is a tension that I think I hear between research and clinical care. A long standing relationship between the researcher and the research population has certain advantages for the prospective consent to get into a study. It also has the problem, which I have confronted in oncology, of confusing very easily in the mind of the patient whether this is research or whether this is really clinical care.

No matter how many times you say it "no benefit

to you, no benefit, you will not benefit, it is simply a toxicity study," they understand something completely different. I fear that if you do have one of the tensions of these long-standing relationships might get better understanding between the patient and the doctor but they have the other fact that you slide, and that the consent then -- the patient understands something different no matter how many times the words are said and how competent they really ought to be.

MR. CAPRON: Right. The longstanding relationship does not have to be with the researcher. I mean, the -- if a researcher in an institution says to her colleagues who have patients in X, Y, Z condition over time, "I would like you to consider exploring with your patients participation in research," obviously you -- I expect you to explore it with them during periods when they are able to comprehend but I recognize that they may be in other periods when they cannot, and those may be the periods when I am interested in studying them.

And after you have determined in this process that they are willing to participate I will then come into the picture, tell them that the research -- and I am not their treater. I am coming in to ask them to be in research but you have got the ongoing relationship with

them and you will be the one who is in a position to say they are able to understand the kinds of things I would be raising or not understanding it.

I do not think we have to anticipate the -- but you are absolutely right. The notion of a therapeutic misconception or therapeutic confusion that arises is pervasive in human subjects research and it is probably particularly an issue with long-term relationships and particularly in relationships where there are difficulties in mental processes.

DR. CHILDRESS: Diane gets the last word and then we will turn it over to Harold. We might even get in a three or four minute break here.

DR. SCOTT-JONES: I just wanted to point out that on page nine and ten of the report there is a pretty good discussion of -- I am sorry. There is a good discussion of varieties in decision making impairment. I think the problem is that when we get to recommendations we lose this complexity and we make the population homogeneous again. But here the various elements that are important, including the situation itself, the particular decisions to be made, all of that is laid out here pretty well. What we need to do is to find some way to incorporate this into the recommendation and not lose these distinctions.

DR. CHILDRESS: Okay. Arturo wants to stick in one quick work.

DR. BRITO: I had been raising my hand here but you could not see me.

I was going to make reference to the same page, page nine, but even there the terminology is tough because I think varieties itself has a lot of implementations. A suggestion that I was going to bring up tomorrow actually because I thought it was more detailed but since we are on the topic, to refer to this section as different or differing levels of decision making ability, and then within that Jonathan, I thought, did a good job talking about the fluctuating ability and the prospective incapacity. But there is one missing here and that is progressive incapacity and progressive prospective incapacity. You refer to Alzheimer's as a perspective but it is really a progressively prospective.

He does discuss under the first paragraph of chapter X where it becomes more complicated because someone put along the two or more of the categories. So I thought it was already addressed and just changing a few of the words around. But you are right, at the end we need to readdress it.

DR. CHILDRESS: Good. We will work on this

some tomorrow. People who cannot be here tomorrow, whether they are on the subcommittee or on the full commission, please give us any suggestions you have. We focused really on one part of the report. We paid most of the attention to that. A very important one and very critical to what we are doing but there is a lot more there and we hope that you will give us suggestions so that we can move forward with the draft.

Jonathan?

DR. MORENO: Can I just say two things?

I have lots of things I would like to say but I have exercised remarkable restraint, I think, over the last hour.

It does seem to me that with respect to research advance directives or whatever you want to call them that this analogy with regard to end of life in a clinical setting is important. Nobody has mentioned one that the investigator has an incentive to sign up subjects and use whatever device is available, which is not the case, although I have tried to convince my physician colleagues it is in their best interest to get their patients signing advance directives in New York I have not succeeded but I think investigators have an inherent incentive to use devices such as this.

Whether that will make much of a difference at all belong in the big picture and I think the stable question that Zeke raised is a very important one and it is an empirical question.

I also want to say that on page 145 the current text does come close to a default position that Laurie and others called for, for family members. It is not in the -- my inadequate chart but is on page 145 and under 5. Perhaps that should be stricken.

DR. SHAPIRO: Okay. Thank you.

I think we are going to have to call an end to this discussion.

Jim, thank you very much. I know your committee is meeting tomorrow and will make use of a good deal of this -- some of the comments that have come up here today.

We are going to take a five minute break because we have to set up the projector and so on, and we will move on to the last two items on our agenda.

Thank you very much.

(Whereupon, a brief recess was taken from 3:11 p.m. until 3:26 p.m.)

DR. SHAPIRO: First of all, let me make a logistical announcement. For those of you that have any

marked up copies of the genetics report, the one that began with the overview and had some outlines of the rest of the chapters and so on, and had the section on religious attitudes done up and so on, would you please make sure to give those to Kathy Hanna before you leave. So if you have any marked copies please give them to Kathy or one of the members of the staff before you leave.

Now we are just slightly delayed by a technological glitch in the projector here. We hope that will be finished in the next few minutes. That means we may or may not get to our last item, which is processes in changing regulations. We may take that up next time. But I want to wait and try to get this done because I know Professor Fletcher and others have to go and I want to get to that as soon as we can. So I will just ask you for your patience for another few moments.

Order, please. Colleagues?

Trish, are you ready?

I want to turn to Alex in a second to lead us through this discussion. Also we have a number of guests who are here to help us with this discussion.

One last change in the agenda. We will with thanks to Rachel's tolerance postpone the discussion of processes in changing regulations until next time.

So this will be the last item of our discussion today so let me turn to Alex.

Alex?

MR. CAPRON: I am getting wired.

DR. SHAPIRO: Alex is getting wired. It is not enough that the world is wired, he has to be wired as well.

(Simultaneous discussion.)

FEDERAL OVERSIGHT OF RESEARCH INVOLVING HUMAN SUBJECTS

(Slide.)

MR. CAPRON: Am I on?

DR. SHAPIRO: You are on.

MR. CAPRON: Is this picking up for you? Okay.

I hope you can all see the screen since we have gone to such lengths to make it project.

One of our basic subjects is the federal oversight of research involving human subjects and we are looking today at a particular aspect of it. Our mandate and the initial focus we took was on the system established by federal agencies that conduct or sponsor research and we recognize that although this part of the report, which is the one that we have seen drafts of so far, is an important and essential and, indeed, we thought without cloning we were going to finish it in the first year. We did not. The so-called federal agencies report.

But there are two subsidiary issues which we are not fully addressing now but which are essential.

(Slide.)

The first is how well are IRB's actually following the rules that are set forth. The second is how well are subjects being protected. Now those are not the same thing obviously. The IRB's can be doing a great job of following the rules and subjects could still not be well protected if the rules were not effective in protecting them. We recognize both of these as topics we want to address but we have not yet fully developed a plan of how we are going to go about that.

(Slide.)

In looking at the federal agency report so far we have seen certain problems. First, there has been an uneven execution of the responsibility to protect subjects among agencies. Second, there is a variation in the amount of attention that agencies give. Third, there has been wide variation in the application of the rules. Indeed, in even understanding questions like what is research, what is exempt. Some of the agencies have looked at things that seemed to us to be research and said, "No, they are not research. We do not have to have IRB's review them."

(Slide.)

At the moment I think it is too soon to reach conclusions and we need to hear from each of the agencies about their own response. Some of the problems are obvious ones but there is one which stands out and that is the lack of an authoritative office to deal with these issues in the federal government.

(Slide.)

So the question that we determined to look at as a whole commission is the one is there a need to have a government-wide human subjects office. We sought advice on this from Charles McCarthy, who is the former director of OPRR, and John Fletcher, who was the first in-house ethicist at the Clinical Center and then went on to be professor at the University of Virginia where he has now recently become emeritus.

We also received additional expert advice from Joan Porter, who reported at our last subcommittee meeting and who is here today again. And from Tina Gonsalus, whose views we have not actually heard yet, who was looking at the additional question that was raised by David Cox, which is whether this opportunity ought to be seized if we are talking about a government-wide effort to say it should also encompass the research which is not federally funded.

(Slide.)

Now it seems to me from the papers that we have received from McCarthy and Fletcher that it is very obvious that the history has very much shaped the present approach to human subjects regulations. In particular, from the 1950's as NIH grew by leaps and bounds the Intramural Research Program was the major focus.

Disregard spelling errors, please.

And within that program normal volunteers did receive an informed consent process and a prior review by disinterested scientists, not by outsiders but at least by scientists who were not directly involved in the research. But patient subjects were not federally protected because, in effect, the studies they were in were regarded as therapy. Beginning in the mid 1960's extramural research grew more rapidly and the process of overseeing the protections was handled by the institutional relations branch in the Division of Research Grants. That was done centrally for all the institutes. That was true of all the negotiations that went on with the institution since research is institution and not investigator based.

(Slide.)

In 1966 Surgeon General Stewart at the time that certain revelations were coming out about problems with human subjects research issued a policy on the

protection of research subjects and made this a responsibility of that Institutional Relations Branch at the DRG. And that office simply followed the pattern that it had already followed in handling the financial and other administrative arrangements in that it entered into assurances with institutions about the way they would carry out their federally funded research and that is where the model of the assurances comes from.

(Slide.)

The DRG put emphasis, as Charles McCarthy reminded us, on education, not sanctions. And, indeed, up until the time of the Tuskegee study there were no sanctions ever issued for any violation by any research institution.

(Slide.)

Dr. McCarthy is a little more sanguine about the extent to which research institutions prior to 1974 actually had some form of internal mechanism and other researchers like Bernard Barber writing at the time showed that many institutions had not yet advanced to the point of advanced prior review of research involving people other than the research community.

(Slide.)

In 1971 the policy that had been established

for NIH was extended to the whole of the Public Health Service and this begins part of the history of the discomfort in this area because the moving force remained the NIH and the IRB/DRG.

(Slide.)

In 1972 Robert Marston, who was Director of the National Institutes of Health, faced with the emerging scandal of the Tuskegee study, which had been a PHS study and not an NIH study but was focusing on the government's involvement in research and with Senate hearings going into a wide range of other questionable research, changed the Institutional Relations Branch into the -- that aspect of their work into the Office for Protection of Research Risks, which he lodged in the Office of the Director.

(Slide.)

At this time there were some in Congress who favored enacting legislation with sanctions for violations of human subjects rights but this was steadfastly opposed by the National Institutes of Health and eventually an agreement was worked out and the DHEW relented on the notion that it should not have any regulations as such. There previously had been a policy, not regulations. They should not have regulations. They agreed they would have regulations and the Senate backed off of the notion of

legislating this. So the provisions of the 1974 Research Act were limited.

It, of course, established the National Commission to study this area but beyond that it established the firm requirement that regulations would be issued that would have informed consent and prior review through an Institutional Review Board and it also made clear that the department had the responsibility to provide consultation and education on the subject.

(Slide.)

The National Commission recommendations which were all forthcoming by 1978 were largely adopted. Of course, children and the mentally infirmed, institutionalized and mentally infirmed were not accepted. The children were later and much more recently adopted.

These became the basis for the 1981 regulations which are really the framework that we still have.

The President's Commission recommended the Common Rule on Human Subjects for protection from all the 20 plus agencies that support such research and that occurred in 1981. A decade later for reasons that Joan Porter nicely surveyed for us that Common Rule was finally published in the Federal Register and one of the things we are still studying is the difficulty in having it truly be

a common rule in application.

(Slide.)

The Office for Protection from Research Risk sometimes found itself subject to direct interference within NIH. In 1992 or thereabouts there was an attempt by the Director to intervene and be involved in some fashion with the Gallo investigation that was then going on for research that had gone on, on the AIDS virus in Africa involving also a French collaborator. This was declined by Dr. McCarthy but there was that kind of pressure that existed.

Moreover, the NIH Intramural Program dragged its feet in cooperating with OPRR on a number of occasions until it was threatened with a disclosure of its failure to have complied with its own federal policy and the threat included the notion that revelation would be made that a subject had died in a sleep study at NIMH. The death was apparently actually not connected to the researchers it later turned out but that threat was sufficient to get NIH to sign on to its assurance.

(Slide.)

OPRR is, however, by the description of Dr. McCarthy and Dr. Fletcher dependent on whistleblowers and the press because it does not really have any institutional

examinations. The Food and Drug Administration by contrast does go out and at least go through a paper trail at institutions. The OPRR, NIH and the other agencies do not.

OPRR has a large case load and depends on outside expertise to -- for most of the scientific evaluation of the cases that are brought to its attention and it has difficulty carrying out major investigations. Dr. McCarthy talked not only about the backlog in investigations but also the impediments that it has to act like an investigatory office.

(Slide.)

To sum up then, the problems revealed by history are first that the Department of HEW and the other agencies or HHS now that sponsors science see research as the primary mission and address human subjects protection only when pushed, usually following a crisis of some sort.

Secondly, that no federal agency holds the position of an authority to ensure the adequacy and uniformity of human subjects protection. Indeed, no one knows how much human subjects research is now ongoing with federal sponsorship much less beyond federal sponsorship.

The Office for Protection from Research Risks that NIH has the informal role of first among equals among the offices and the different agencies, it has by far the

largest number of projects, but it does not have staff or authority to exercise actual power over the other agencies.

(Slide.)

Third, the oversight of protecting human subjects is delegated to research institutions because of that history of the assurance process and those institutions themselves obviously have conflicts of interest in wanting to see research go ahead rather than being overly concerned about human subjects protection.

The assurance process has by now become routinized and you can see why. A relatively small office has responsibility for almost 450 multi-project five-year renewable assurances, 3,000 special projects, single project assurances, and 1,500 cooperative research projects. And as a result fewer resources are available today for its traditional educational function.

(Slide.)

Sixth, despite some differences, and I think this was interesting because we were looking for people with contrasting perspectives, despite some differences and emphasis both McCarthy and Fletcher agreed NIH and the rest of the Public Health Service has not strongly supported formal processes for human subjects protection.

(Slide.)

When asked, they refused to provide material support for the process of developing the Common Rule, which eventually ended up in the Office of Science and Technology Policy, and it has been slow to comply with OPRR findings and the terms of its own multiple project assurance.

(Slide.)

So looking at the recommendations we got from our two principal experts, first McCarthy recommended the creation of an Office of Research Ethics within the Office of the Secretary of Health and Human Services to have three divisions. One concerned with human subjects protection, which is our focus. And then another with animal, laboratory animal, protection. And a final one of Scientific Integrity, another issue which has engaged the scientific community and the National Academy of Sciences and so forth in recent years.

(Slide.)

He also said that the Human Subjects Protection Division should have at least two branches. The first an education branch and the second a compliance branch. And that the office should make an annual report to the Congress which would include a report on the performance of

not only all the agencies within the Department of Health and Human Services but all other federal departments and agencies. It would, therefore, have government-wide authority even though it was lodged in the Office of the Secretary of HHS.

(Slide.)

And that the Director of the Office of Research Ethics would submit his or her own statement of personnel and budget needs to Congress independent of the HHS submission.

(Slide.)

John Fletcher recommends the creation of a National Office of Human Subjects Research advised by a national advisory committee on human subjects research made up of 11 to 13 people from outside government. This is in line with the recommendation made by Jay Katz a number of years ago actually when this commission was being empaneled when he said, "You do not need the National Bioethics Advisory Commission, what we need now is a group that would actually have continuing oversight of the administration of these rules."

(Slide.)

Fletcher also said that the National Office of Human Subjects Research would have government-wide

authority and made analogies to the Nuclear Regulatory Commission and the Office of Governmental Ethics. And the Congress would appropriate funds directly for the NOHSR and the Senate would confirm the Director nominated by the President.

The office would have authority to sanction violations of the regulations.

(Slide.)

And then going beyond the type of the office to oversee government sponsored research Fletcher recommended,in line with David's suggestion and something we are going to hear more about from Tina, I guess, is the extension of the oversight of the office to all human subjects at least as to the basic provision of IRB review and informed voluntary consent.

(Slide.)

Now we need to look at these recommendations and say what are their strengths and weaknesses. For the McCarthy recommendation the strengths seem to be that lodging this in the office of a major department of the government gives it protection because the Secretary is a powerful figure in the United States Government and the office, therefore, is not standing alone but has the protection of the Secretary. And it would also make

absolutely clear that sitting at the head of HHS that office has authority over all divisions of the Public Health Service, which ORR struggles to exercise today.

The weakness is that it does not fully remove the conflict of interest because it leaves the office within a department which is the major sponsor of research by the government and it compromises the independence of that person because being a part of the Office of the Secretary, whatever independence one may have, is somewhat dependent on the forbearance of the Secretary who may not be happy with everything the office is suggesting.

It creates the problem of a department having an office which then has oversight over sister departments and agencies.

(Slide.)

Looking at the Fletcher recommendations, the strength is that clearly this office would be independent of the research sponsors and it would benefit from an outside board which would bring not only expertise but visibility to the subject. It would not be just a group of government employees. They would be responding to and seek the advice of outsiders who would have the ability to raise the issue publicly under the Federal Advisory Committees Act.

The weaknesses are that, you know, we clearly need White House and/or -- probably and as well as or -- real sponsorship. If the White House is not interested in protecting this office and if a committee of Congress or certain members of the committee do not regard it as an important function that they want to protect and ensure its independence, a small office like this will not have independence. The press alone cannot ensure the independence of an office like this.

Furthermore, absent some current human subjects scandal it may be difficult to create a new agency in our present smaller government era.

(Slide.)

Having said this I also want to suggest for our discussion that there is certain things we can focus on and other things that we can exclude. The central objective I hope we could agree on would be to create a body with authority and ability to get the job done. Although OPRR is the major human subjects protection body today, its performance need not be the focus of any report. Indeed, I would suggest it would be inappropriate to focus in on OPRR. The concern is with structural problems, some of which affect OPRR's operations, some effect its location, and likewise the location of comparable offices in either

departments. The concern is with all federal agencies and just looking at OPRR would wrongly focus us on NIH.

(Slide.)

Also, our present mode of operation, and all the concerns that have been raised about the assurance process and the adequacy of IRB's, need not figure as a topic for us in this report. We have committed ourselves to the notion that that is a topic that needs to be studied. Were there to be such an office, either at the secretarial level or as an independent agency, certainly it would be appropriate for that office then to take on this responsibility and maybe continue the present format and maybe modify it.

But our satisfaction with or questions about, or our dissatisfaction with the current method of assurances, and the use of IRB's is not something we have to determine and I think should not really be a subject of debate while we are deciding do we need a government-wide agency and/or any of these models the ones that we should follow. I think that would be a distraction.

(Slide.)

Likewise, if we believe that the office should have government-wide jurisdiction we might -- and yet we are unable to see or unable to develop private enthusiasm

for bringing their research under such an office we might say, "Let's see if it works on the government-wide basis and then as a later issue that office could go to the Congress, assuming that Glenn bill does not already pass, and say there really are issues with privately funded research and the best way to ensure that is conducted in an appropriate way is to bring it under this office.

Finally, one point I did not put up here but I think is obvious, when one talks about this office I think it is best not to use the elocution that we used occasionally at first, which was "elevating OPRR to."

Both for the reason I do not think we should solely focus on OPRR but it is very likely that just as the departments have their own ethics offices now to deal with the conflict of interest and so forth administratively within their office or agency, and yet there is a government-wide office of governmental ethics it is very likely that we need a governmental-wide policy setting, rule interpreting and maybe investigating body, and an agency by agency ability to work with their own grantees and their own researchers to get how the rules apply and the process of giving the grants and so forth. All that remains.

It very well may mean that only a small part of

what is now done in any of the agency's own office for protection of research subjects would be transferred over. Those offices really have ongoing responsibilities but the overall educational, interpretive and public visibility issues would really be handled by this other office.

I was struck not only by the very high quality of the papers that we have gotten but also by their very surprisingly large congruence. I think that it would be useful for us to focus on some of the almost political issues that arise in one approach rather than another if we can first agree on the overall objectives.

Thank you.

DR. SHAPIRO: Thank you very much for that very helpful presentation.

I would like now to turn immediately rather than go to -- I hope you will forgive us, Alex -- rather than turning directly to discussion to some of the issues you have raised I would really like to turn to our guests and see what comments they would like to offer.

I know Professor Fletcher has to leave shortly so I would like to turn to him first and see what further comments and/or advice he might have for us at this time.

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E V E N I N G S E S S I O N

DR. FLETCHER: Thank you, Mr. Chairman.

I was very impressed with Alex's laying out of the issues. I did not disagree with any of it. I was struck with how much Charles McCarthy and I did agree on since we do have different perspectives but I think our main difference is one of political philosophy, if you will, that he wants and expects the success of the body that he envisions, which essentially is the same body that I envision except with the outside advisory committee. His does not have that.

He feels that in the real political world a government-wide body with these responsibilities could not succeed without the protection of a powerful secretarial member of the cabinet.

I agree with the point that Alex made in his comment on the weakness of the McCarthy proposal is that it does not remove the conflict of interest.

I think that the degree of the weakness of the present system, the weakness of the present system that we have, in protection of human subjects is influenced -- I want to choose the right word -- somewhere between moderately and heavily because obviously OPRR's position in the whole scheme of things is not the only problem. IRB's

are the problem. The lack of available resources within institutions, federal agencies, universities, of persons with expertise to lead this effort is a problem.

But I do think that it is -- the conflict of interest and the conflict of missions is a kind of persistent weakness that demoralizes the whole system. I have been aware of it all of my adult life from the time that the solution was invented in the early '70s to have NIH effectively regulating itself. And if you have that kind of central conflict of missions and conflict of interest it is the kind of national commentary on evading the problem.

So I would say even in an era of smaller government that leaders in Congress and the American people are interested in better government, to have smaller and better, and there is not an enormous new amount of appropriations to be made in creating a new body and going about doing this right.

So I would say that the McCarthy plan is a good one except that it lacks the national advisory committee feature but it is in the wrong location. The location still begs the question and if it is put there it will continue into the next era, the kind of demoralizing effect that has produced such lack of respect, particularly from

within the federal sector, in looking down on our present body, the OPRR.

I think that the commission should take a strong position and my recommendation would be to take a strong position in overcoming this conflict of missions, structural conflict, as a violation of -- it is a violation of the principle that Congress used in adopting the legislation of the National Research Act, which was to put the interest of research subjects first. And the basic problem is that the location of OPRR in government or of the McCarthy plan in government still evades the deeper ethical principle on which the whole system rests.

If you have a contradiction at that basic level that is not really an acceptable ethical solution to the problem that we are in.

DR. SHAPIRO: Thank you very much. Thank you for those remarks.

Let me turn to our other guests again before turning to members of the commission.

We have got someone who has traveled all the way from the middle part of the country, Illinois, so let me turn to you, Ms. Gonsalus.

MS. GONSALUS: Thank you. It is a pleasure to be here. Since you do not have anything in writing from me

I will take a few minutes to lay out --

MR. CAPRON: You have to get on top of these microphones.

MS. GONSALUS: Okay. How about now? Have I done it yet?

(Simultaneous discussion.)

MS. GONSALUS: Since you do not have anything in writing from me I thought I would take probably four or five minutes to lay out the path that I have followed and the kind of advice I am going to submit to you. I would welcome your reactions to it.

By way of self-disclosure I think it is important to tell you two or three things about what brings me to this place and who I am and what I do. I am a parasite on the research system. I am a university administrator and a lawyer. I am pure overhead. That is one of the most important things.

In that capacity what kind of work do I do? The kind of work that I do -- in my university I am known as the Department of Yucky Problems. I got a promotion last year and now I am Department of Yucky Problems and Streamlining.

The kind of yucky problems that I do --

DR. DUMAS: What kind of problems?

MS. GONSALUS: Yucky problems.

DR. CASSELL: Yucky.

MS. GONSALUS: Yucky problems.

DR. DUMAS: Oh.

DR. CASSELL: Hold it in your hand.

MS. GONSALUS: Okay. We will keep working on this.

Yucky problems.

DR. DUMAS: Yes.

MS. GONSALUS: Which means that I come from what I call the train wreck school of professional ethics. There is a problem, a train wreck, there is bodies, there is blood, there is people screaming and crying, there is mess on the ground, and that is my job. I go and deal with it. That means that I have had a variety of internal compliance related responsibilities, problem response.

My major professional interest is in how do you conduct effective and credible internal investigations inside an institution when you have a number of conflicts of interest built into the system. How do you go about doing an effective and credible job of self-regulation, professional self-regulation? So that is where my major interests lay.

I look at the problems. I try to solve them as

best I can and then we try to go on, and then we try to look at and review and improve, if possible, both the policies and the structure that were in place when the train wreck occurred to try to prevent future such events. So that is my professional interest and how I come to be here.

I also served on the United States Commission on Research Integrity, which also informs my view on perhaps some of the actions that you should take or not take, and I will come back to that at the very end of my remarks.

I was asked to look at the possible unified government's federal and private human subject research under an OPRR-like structure. Let me just discuss some of the issues of the OPRR-like structure. I understand that you as a commission unanimously passed a resolution in May that no person should be enrolled in research without the protections of informed consent and an independent review of the risks and benefits of that research.

I understand that you have had a form of Presidential endorsement of that concept by saying that no American should be an unwitting guinea pig in experimentations putting them at risk.

Conceptually, therefore, I think that where I

started in this task was to say if you take our current definition of research and apply it globally to all research involving human subjects what happens. I remind you that given the kind of work that I do I bring a relentlessly practical perspective to these issues. I am not very good at the concept. I start with the immediate problem.

So instantly practical problems began to intrude into my examination of these issues. The current definition of research is quite properly, I think, very broad. "Systematic investigation designed to develop or contribute to generalized knowledge where you obtain data through intervention or interaction with subjects."

Global applicability of that definition could sweep many activities into its scope that encompass very little risk, little or no risk. And so one of the questions is how remote must the risk of serious harm be in order to encompass an activity within the definition of research and, therefore, the regulation of it and, therefore, a system that requires paper, and people, and oversight, and costs, and benefits. How do you balance those issues?

So very early on there would have to be an effort to design exemptions. We right now have six

exemptions for things that require prior review. There would be very serious work involved, I believe, in designing appropriate exemptions. If you think about the definition broadly applied to all activities the current definition of research you could arguably -- you would encompass many activities of polling organizations, market research, arguably some forms of journalism, as well as the things that are obviously considered research. The kinds of things that are of the most concern. For example, some of the in vitro fertilization clinics and diet clinics. Some of the things that you immediately think of when you think of as unregulated research, health services research, internal evaluation research, corporations that are looking at how do their employees like one thing or another about the company. There are a whole variety of things that could be encompassed under the current definition.

So examining carefully the prospect of serious harm, how small is it, is it small, versus the cost of regulation is I think the most pressing important issue. I think that one could design appropriate exemptions with appropriate work but that raises a second category of practical problems which I have to tell you is really hanging me up.

Who determines the applicability of the

exemptions? Clearly in terms of a basic principle you do not want the person who is performing the research, him or herself, to be deciding that the research is exempt so there has to be some level of review. Who does the review? How much paperwork? Do you need to assist them? Do you build in an incentive for a much larger system of for profit IRB's? Do you build an incentive for a system where you have pristine paperwork and you have lots of people completing paperwork and reviewing things and filling out forms? And the very serious ethical issues sort of get lost in shuffle because you have diluted the effort so much.

Do you have this -- I mean, I could imagine developing an immaculate extensive system of paperwork that had no meaningful ethical review in it. I have seen IRB's function that were very, very good at the paperwork but spent no time talking about what I think are the issues that an IRB ought to grapple with.

So the question is would expansion divert valuable resources and valuable energy and how do you avoid that outcome? The danger is creating a burdensome possibly profit driven rubber stamping system diluting attention to the serious ethical issues.

I could go on about the problems that I ran

into but having sort of come to that point I decided to stop and go at it from a different perspective, which is rather than making it global with the current definition, to take a better system of encompassing all federal agency research, which I believe is addressed in some of the reports that you have had, and then adding in on a list basis -- I am not fond as a principle of laundry lists and I have strenuously opposed the laundry list approach to definition of research misconduct. But I did explore taking -- just listing known areas of research that put human beings at risk and adding those whether conducted privately or publicly to the scope of federal oversight.

Gary Ellis has defined seven areas in some of the letters that he has written and he wrote me a letter and he sent some copies of these. He made a presentation at the PRIMER meeting recently where he defined seven areas that are beyond the boundaries of existing regulations that are places that questions have arisen and where there are people potentially at risk.

Colleges and universities not receiving federal research funds, some <u>in vitro</u> fertilization clinics, some weight loss or diet clinics, some physician offices, dentist offices, and psychotherapists offices.

One of the examples is the dentist who decides

to take out of the next number of patients that he has the fillings on the theory that he is conducting a form of research. Does he know it is research? Maybe and maybe not.

Some legal services clinics. On my campus we have some very interesting examinations going on in our clinic at our law school about when are you actually conducting research. When you are taking students, you videotape them, you teach them how to interview clients, the clients give their consent for the interview, but then you go on, you train other students with it, and then you start doing research on how do you generalize this knowledge about this sort of interviewing and how do you use these. Pretty interesting questions that they are exploring.

Some corporate and industrial health safety and fitness programs and some developers of genetic tests.

So my current thinking is that rather than taking the global approach with all the practical problems that entails it would be superior to start with the known problems, add them in, take a cautious incremental approach where you can document the cost/benefit ratio, that official cost/benefit ratio of adding in some regulatory system rather than taking a sweeping approach.

I think that you have to focus on the goals of protecting subjects from risk, the unwitting participation aspects, and again on the focus of informed consent an independent review where you know that there is a danger of risk.

So then the question is how do you reach that within the available resources consistent with reality. The paradigm that I think is applicable that I use in thinking about a lot of the problems that I deal with is one that was first introduced -- actually I heard Bud Relman give a presentation probably 15 years ago and he used the term "low incidence, high severity problem."

The serious problems do not occur very often. When they do occur they are very, very serious.

So what is the low incidence, high severity problem of this nature? What sort of response does it suggest?

To my thinking of low incidence, high severity problem the most sensible approach is that you put almost all of your resources into education. Most people most of the time want to do the right thing and you have to make sure you know what it is. We do not have adequate resources in our system for that right now.

The second thing you have to do after education

is that when you have problems you have to respond to them. We have very serious problems in the research community and in the academic research community with designing appropriate responses to problems. It is a fundamental problem of professional self-regulation. We have -- it manifests itself both in how the universities respond and also how the federal government responds.

Inside universities -- I was at a conference a couple of years ago where an IRB executive secretary was talking about a system they designed on their campus for tracking the publications of researchers on their campuses and then trying to correlate them with IRB approved protocols, which raised a firestorm of protest on campus at the big brother concept.

In the arena of research misconduct any time we talk about government regulatory mechanisms and government oversight we can invoke the specter of the science police. The science police are going to try to destroy research as we know it.

There is serious resistance to any kind of inspection system. Now it is widely accepted that we could have an inspection system for animal sites but the concept of having inspection for human sits is anathema.

And the third issue -- and the third thing --

is you have education, you have response to problems, and the third thing you need, I think, for a low incidence, high severity problem, is to have penalties for violation because I assure you that many, many people are busy. They have lots to do. And no matter how well meaning they are and no matter how much they believe in theory in the ethical issues if it is demonstrated time and again that there is no penalty for a serious violation people have better ways to spend their time than to fuss with this nonsense.

So that is the three things I say.

This leads to two issues and I have brought my conclusions. There are resource issues that someone is going to have to grapple with because the current structure does not have enough staff and not enough money, and probably not enough power to engage in either any of the education response to problems and penalties for violation that does not exist presently.

And then we have the structural problems and there are, I think, disabling existing structural problems that must not be perpetuated as we move forward into doing better.

The first is the structural conflicts of interest identified by Dr. Fletcher and Dr. McCarthy.

The second is the insufficient resources issue that there are not enough resources for the current mission in terms of IRB's that do not work well. You have earnest people engaged in an inadequate and insufficient review process. You do not have adequate education of PI's. You have research that just flat out has not been submitted for review because somebody does not conceive that he or she is conducting research. And then you have review systems that do not work very well. The behavioral sciences I think are a perfect example.

The third disabling structural -- existing structural problem is the uneven application and the uneven jurisdiction both within federal agencies and then beyond to universities.

I think the most likely answer is a different governmental status and structure in budget, single standard, single office, but a single office with some kind of decentralized or distributed system where you have a single standard, a single office, but it works in a distributed way within the agencies along the model that was just discussed.

I think there are some very fine models to explore. The Office of Governmental Ethics I think is the prime model worth exploration.

Gratuitously I am going to add a final note, which is that I think that it is your job, in fact, to explore and to try to solve the structural problem and to make a very explicit recommendation about what the structure should be and I hope you will retain really solid experts who understand the political realities to give you advice on this to help you devise a structure that will work, to find the proper niche, to find the proper reach, authority, jurisdiction, the proper budgetary protection, the right clout to get action when needed.

I will tell you that from my experience on the Commission on Research Integrity, which I would call mixed, I would say that as you work it is extraordinarily important to think about to whom your report is submitted. Who receives your report and how exactly will it get implemented?

What will be done with it?

If you make sort of a generic recommendation somebody should think about this and improve the structure you could be looking another two, four, five, six, ten years, never for actually making a difference in how this works. I cannot believe that this number of really busy, really expert people should put in that kind of effort for that kind of result.

Thank you.

DR. SHAPIRO: Thank you very much.

Ms. Porter, is there anything you would like to add to what you told us last time, which was extremely helpful to all of us?

MS. PORTER: I think I would like to address a little bit different focus that might help in making some decisions on where the best locus for a federal office to oversee and to regulate human subjects protections would be.

I actually have a handout and some overheads that are very brief, mercifully and uncharacteristically, but I think they help.

DR. SHAPIRO: Please.

MS. PORTER: We did not collaborate before we came together today, the various presenters, but I think you will be struck by the amount of compatibility there is amongst the presentations even though the approach is somewhat different.

(Slide.)

I thought that it might be helpful to the commissioners to try to decide on what the goal of a federal office would be and then use those goals to inform the best location for the accomplishment of those goals.

I have put together two sets of goals. Goals that a human participant in research would expect the federal office for protection of human subjects to carry out and then the second overhead will give a list of goals that I think any entity regulated by a federal office for protection of human subjects would carry out. I did not address animal welfare issues in this particular presentation.

(Slide.)

First of all, what should a human participant in research or any other member of the public for that matter expect from a federal regulatory office for protection of participants in research? I think, first of all, and maybe these are not in my priority order, these are based on my values, there is considerable overlap between what an individual would expect and what an institution or an entity would expect from a federal office. Maybe you would choose to put different goals on here or take some of these goals off but I think it is the starting place.

First of all, an individual participant in research would expect easy access to information on rights and welfare as research participants and some support in exercise of those rights. I think the person would expect

adequate and timely information to and education for those entities regulated concerning protection of human subjects in research. They would expect that the organizations carrying out the research had been informed about what they were supposed to do and guided in what they were supposed to do.

I think the individual would expect adequate and consistent -- at least minimal protections in research regardless of the source of funding or support. Obviously we see that this is a major issue. How far is this office going to regulate? As far as it does now or is it going to take on all research regardless of resources, or support, or funding?

I think we have to start thinking in this direction. I think in this day and age it is not appropriate to ask individuals to try to sort out is it federally funded research or is it under a state law or is someone looking after my rights and welfare, or is it one of those seven categories which were alluded to that simply fall between the cracks.

I also think that the individual would expect timely and consistent investigations of allegations of noncompliance with human subjects protections by both regulated entities and the investigators. And then, of

course, responsible follow-up -- follow-through on findings of noncompliance with human subject protections by regulated entities and investigators.

Then I would believe that the individual would want an office that was there to carry out actions that would be consistent with promoting protection of human participants in research in an as political a manner as possible. That is an office that would stand as a champion of human subjects rights and welfare above other goals that might be competing and that were inconsistent with that goal.

For example, we heard this morning a discussion of the use of tissue samples and the idea that, oh, it would be a tragedy to lose this important invaluable research but it may also be a tragedy to collect information or use information that represented a violation of the rights and welfare of individuals. So there has to be some office that is a champion for human subjects protection in the milieu of larger competing issues or different competing issues, or resource demands.

(Slide.)

Likewise, I think, what would an entity that was regulated by a federal central office expect? I think they would expect many of the same things, of course. They

would want adequate and timely information and education concerning protection of human participants in research. They would want guidance and help in knowing what they were supposed to and how to carry it out.

I think the regulated entities would want to have an office that was able to ensure well developed, broadly open and proactive policy development and regulatory interpretations and modifications. Somebody that was really well connected with what was going on in the world in terms of new technologies, development of new data collection systems, and certainly it is going to be more than just federally conducted research.

Someone -- some office that understood the health care delivery system very well because much of our research will be coming from our health care delivery system as we move towards more managed care systems and consolidated systems of health care delivery.

The regulated entity, I would expect, would want the federal office to have the ability to coordinate the federal organizations supporting or conducting research under the Common Rule. They would want some kind of ability to ensure appropriate consistency so that all of the federal entities were not going off in their own direction.

They would certainly want fair and consistent enforcement of the regulatory compliance authorities. I have added here, but you probably cannot read it, including feedback to the regulated entities on the pitfalls to be avoided. If entities are in noncompliance we owe them and other entities an explanation of why that is the case and try to put in some corrective measures.

And then I think another goal would be to have actions again consistent with promoting protection of human participants in an as a political a manner as possible. Try to keep it shielded from politics and other goals that divert us from really protecting people who are involved in research.

Lastly, I think the regulated entities would have some expectation of minimization of paperwork and other administrative burdens consistent with the accomplishment of protection goals. I also think an important goal to preserve is decentralization and having decisions made at the local level and the benefit of understanding the local milieu so that there was not a big centralized group that would dictate but that would have an open system that would ebb and flow and collect information and develop policies and procedures that could be applicable but would help from the local perspective.

All of this, of course, would require adequate numbers and quality of staff. Other adequate resources, creativity, credibility, visibility, openness, compassion, energy, and sufficient independence and authority to effect these expectations.

I think if you would take these goals or others that you might come up with and crosswalk them with different organizational options it might become more clear what was the preferable locus for a federal office for oversight.

We do not have to be gurus at public administration to understand that there is a formal organization and an informal organization. In some of the most irrational organizational locations effectiveness can happen, productivity can happen, and even at some of the most ideally placed organizational levels apparently sometimes things do not get done because there are so many unanticipated consequences.

There are perturbations from the environment that we do not expect and so something that looks ideal on paper might not work either. But I think our goal is to try to come up with the best place to maximize what needs to be done and part of that is deciding what needs to be done and coming to some consensus on that and then moving

on.

I think Dr. McCarthy's suggestions, I think Dr. Fletcher's suggestions, both have pros and cons. Some of these goals would be better addressed in the organization that Dr. Fletcher proposes. Some would be better addressed in what Dr. McCarthy has proposed. But there may be other permutations and alternatives too that could be laid on the table.

CONCLUSIONS

DR. SHAPIRO: Thank you very much. We very much appreciate your second appearance here. Thank you very much for your help.

Well, in view of the lateness of the afternoon, we have run rather later than I had hoped, I am going to ask the committee's indulgence and forego any further discussion of this topic at this time.

Eric, you will just have to excuse me.

But in any case -- but I really -- perhaps those of you who will be here tomorrow can certainly take that topic up again.

I want to thank our guests especially.

But before adjourning I promised that I would give Zeke a moment to say a word or two since this is in

all likelihood his last meeting as a formal member.

DR. EMANUEL: It is absolutely my last meeting.

This is my lasting meeting and I wanted to take a minute. I am resigning from the commission not for any reason of dissatisfaction. Quite the opposite. As has been alluded there has been a major trade between the NIH and NBAC. You got the better of the deal. Eric is coming to you and I am going to the NIH.

DR. SHAPIRO: We also have a future draft choice.

(Laughter.)

DR. EMANUEL: This is my last meeting and I wanted to -- I assured Dr. Shapiro I would take only a few minutes.

First, I wanted to thank the staff for having put up with a zillion requests and all sorts of irrational demands and doing it with grace and very promptly under difficult circumstances.

Mostly I did want to thank Dr. Shapiro for being a wonderful chairman and for leading us without bamboozling us with any agenda, and for really, I think, helping us along.

I also do want to thank my fellow commissioners.

I want to reiterate something that Eric said earlier in the day, that this really is a wonderfully collegial group. We have a lot of big people with a lot of very strong and well developed ideas that do not always agree as we have seen today. And yet there is, through all that diversity, an attempt -- first of all, a respect for each other and, second of all, an attempt to come to some kind of constructive consensus. We saw that in the cloning report and we have seen it today in these two different reports.

It is really marvelous to see especially in a day when -- an era where cross fire is more the model rather than, I think, this constructive consensus building and trying to move forward in a wonderful way. I will miss that and greatly appreciate it and I hope it is something that is preserved with future selection of commissioners because I think it really is a great model.

If I could take one more minute, which is as I walk out the door my little look at the future. I think we have spent a lot of time today on it and it was number one on Eric's list, which I spent two weeks in England and part of what I was doing is thinking about where would I like this place to go. I really do think the IRB issue, this protection issue, actually getting it to work is really the

key issue.

It is not sexy in a way but in the nuts and bolts it is the issue.

We keep resorting to the IRB for all sorts of reasons suggesting it is a pivotal function. It is doing a pivotal thing. We cannot get rid of it and we need it more. Yet there are excessive demands on it. It was built 20 some years ago and not built for the current era. We know that it is only going to get worse. The NIH budget is going to go up. More research is going to be done. We do not have a good understanding of how it works in practice as you have heard today.

Most importantly and distressing in my opinion is the public has no idea that it even exists and that actually they are being protected. So I think actually if this commission focused in on that problem it would be of great, great benefit to the whole country. I think this issue of where protection sits is one part of the puzzle but only one part of that other puzzle.

So I really do greatly appreciate having been able to serve a year and a few months with all of you and it has been a wonderful experience for me and I thank you very much and look forward to whatever future interactions we have.

(Applause.)

DR. SHAPIRO: Zeke, on behalf of myself and all the commission members and the staff, thank you for all the contributions you have made not only to our reports and to ourselves, and to our work but to each of us as we worked together over this time.

So we look forward to interacting with you on some basis that is appropriate as we go ahead.

With that, we are adjourned.

(Whereupon, the proceedings were adjourned at 4:33 p.m.)

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