28TH MEETING

OF THE

NATIONAL BIOETHICS ADVISORY COMMISSION

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SHERATON PREMIERE AT TYSONS CORNER
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I N D E X

P R O C E E D I N G S

OPENING REMARKS

DR. SHAPIRO: Okay. Let's get our meeting underway. We have some time early this morning devoted to just an update on our International Project which we have not touched base with for quite a few meetings now and then we will return to the issues that are before us from yesterday's meeting needing some further resolution.

We will turn, first of all, to the HBM report and go as far as we can with that. And, however, we are very anxious to return to have some time left over to return to some of our discussions regarding human stem cell because, while I am sure we are all in a somewhat different place on this issue right at the moment, I wanted to make sure I understood where we left off yesterday with both cases -- what we termed cases one and two. And, particularly, an aspect of Dr. Fletcher's suggestion that in addition to one and two that we think about relaxing, I think was the word we used, the ban on embryo research so that that could be conducted also with embryos from that particular source. I want to make sure I know exactly what I feel about that issue but I am not

exactly sure that the commissioners have focused on that and I am anxious to get your view on that.

I, also, want to go on, hopefully, if we have time today to cases three and four since we -- it is my own personal view -- we have not spent enough time thinking about why it is we feel one way or another on those issues but I may be speaking only for myself on those issues. I have some serious uncertainty about how we can so easily separate one and two from three and four but in any case we can come back to discuss that if time allows. If not, we will have to discuss it at our next meeting or through communications between meetings.

So let's now just turn immediately to the International Project.

Eric?

DISCUSSION OF THE INTERNATIONAL PROJECT

DR. MESLIN: Thanks very much. The commissioners have in their briefing books an update on the International Project, which includes the short outlines of five contracted projects. You will recall some meetings ago the commission encouraged us to start to gather empirical data to support the conceptual or

regulatory analysis that we would be providing which gives some indication of the nature and extent of research being conducted and funded in other countries by the United States and principally what a number of the ethical issues are as experienced and perceived by investigators, IRB's and others.

We have, I think, quite a stellar cast of extremely knowledgeable and experienced and well-informed investigators working with us. Two of whom have kindly agreed to come today and give us a brief update on their progress.

Alex Capron has taken the commission lead on this issue, as have a number of our staff. We have been engaged in conference calls to update ourselves.

The timetable for this project is principally dependent on when the research gets completed but we are obviously hoping to have the main empirical work completed by the end of the spring or early summer. Obviously, issues of how long the commission will be functioning and how much work we can get done bear directly on that.

I should, also, mention at the moment in the audience with us today is Dr. Gerald Keusch, the new

director of the Fogarty International Center at the NIH and if time permits I would like to ask Dr. Keusch to give us a little update on what Fogarty is doing. Hopefully, we will have a chance to do that.

But at this point let me just ask Dr. Sugarman and Dr. Kass to come up and join us. It is a very informal session.

You have in your briefing books lengthy descriptions of their biographical backgrounds so I will not spend a lot of time rehearsing that except to mention that Dr. Sugarman is at Duke University and is leading a project in other countries, which he will describe, and Dr. Nancy Kass is at Johns Hopkins University, who is concentrating on work within this country, and I will let them give you a more thorough description.

Although the agenda says 15 minutes for both of them, I think both protocol and politeness would, I think, dictate that they can have certainly an even 15 minutes each. We certainly did not want to rush them. And then we will have ample opportunity for discussion.

So I think we can begin with Jeremy.

Thanks. Thanks very much.

UPDATE ON STATUS OF CONSULTANT PROJECTS

JEREMY SUGARMAN, MD, MPH, MA, DUKE UNIVERSITY

DR. SUGARMAN: Thanks for having us here. It is a pleasure to talk with the commission as a whole about a project that has been worked on and designed and being refined over the last few months.

DR. SHAPIRO: Excuse me. You probably have to bring your microphone closer especially so people behind you can hear.

DR. SUGARMAN: Is that better?

DR. SHAPIRO: Contact your adenoids if possible.

(Laughter.)

DR. SHAPIRO: Can people hear back there?

DR. SUGARMAN: Is that a yes? I cannot --

DR. SHAPIRO: Yes. We can hear.

DR. SUGARMAN: Is this one better?

Okay.

As I was saying, it is a pleasure to have the opportunity to discuss with the entire commission a project that we have been refining and developing over the last several months. This is a project that is contracted

to Duke University with a subcontract to Family Health International, which is an organization which has conducted lots of international research.

DR. SHAPIRO: Jeremy, right into it.

DR. SUGARMAN: Okay.

DR. SHAPIRO: It is like a rock star. That is it.

DR. SUGARMAN: Okay. So the project involves a series of case studies. Specifically eight international case studies. The goal here is that we get an in depth look, where possible, of these eight international sites to try to find out what the experience is with research that is funded with U.S. funding and when these research projects are going forward; and when the U.S. regulations are coming to play, how do the U.S. regulations correspond to the international investigators' own moral rules or ethical standards; and when they do use our standards or their standards or a combination of those standards, what happens if these rules come into conflict, how do they reconcile them in the day-to-day practice; and finally what recommendations do they have as sort of experts in their own cultures about how research funded

with U.S. funds might be improved in order to make the research more consonant with their own understanding of moral and ethical rules.

What we have done in order to meet logistical and budgetary constraints is do two rounds of site visits. We just completed a first round of site visits done by senior staff, which were intensive designated visits to try to design site visit guidelines to be used in the subsequent round of visits.

In the subsequent round of visits what we are doing is we are piggy backing these visits on top of already planned trips from FHI personnel who go on a regular basis to study sites. They have established relationships with investigators throughout the world so what we are doing is then training the FHI site visitors in the techniques that we want them to use to be able to construct a case study that meets the domains of the project.

What we do is we identify one local person as our primary respondent and that person gives us a contact or tell us, "I do not know the answer to that question about how the research is done in country X or Y but this

person can help you."

We have had the opportunity during our first three visits, which were Chile, Kenya and Taiwan, to speak with local researchers institutional review board members, people who obtain informed consent, and members of existing sort of national research ethics commissions.

So what we try to do is set up the visit in advance. We talk to the respondent and say, "Who should we talk to while we are here," and we try to flush out that picture.

What we are going to do to assure that these site visitors who begin round two sort of use the same approach is to have a joint training session where the site visit guidelines will be reviewed, the domains of the project explored, and we will share with them our observations at trying to gather these data quickly, efficiently and accurately. That is scheduled for March 12th and Patty Marshall, who is working on another project, will be assisting with that.

And I have to say that both Patty and Nancy Kass have commented on our initial site visit guidelines so that there is some interrelationship among the projects

that are being done in the International Project.

The upcoming site visits are to Mexico, Haiti, England and Bangladesh. These are tentative. It all depends on whether these site visitors can go depending on the timing of their trips. We may need to adjust that over time but we will do something like that. We are trying to strive for some kind of geographical representation as much as possible.

What have we found so far?

Each of the three trips has been incredibly rewarding. When we gathered to meet to discuss the trips we learned a lot. I have to say that I am sharing with you these observations. We may change our opinions about these over time as we reflect on all the other experiences that we garner so they are very preliminary but we found an awful lot of interesting things.

With respect to the domain about the experience we clearly went to places, targeted places, where there was a lot of international experience. Some of these places have experience working with other governments as well as the United States Government and they sometimes reflect on the differences of what it is

like to work with U.S. investigators, European investigators, and the like.

What was surprising despite what headlines read a lot of the time is that there is an awful lot of similarity in each of the three places between our regulatory apparatus and rules and what they believe to be true. Now there are some differences.

They also feel at each of the three sites we went to that there is an importance of compliance with local standards as well as sort of the international standards that some might say would be imposed but they did not see so much as an imposition as sort of a way of doing things.

We frame and the media tends to frame the sort of scandals of international research in terms of conflict of moral rules yet we found it very difficult in each of the three sites to elicit conflict. What happens if they conflict? And in each of the places we went there was a lot of story about negotiation rather than conflict and compromise. That was acceptable compromise and negotiation realizing that they were competing forces and just had to come up with a solution.

They shared many of the attributes of research. It is not surprising we have international codes of research ethics, I guess, that there was a lot of shared understanding. But, very interestingly, certain aspects of research design seem to play an important role in different cultures.

For instance, in Taiwan, they abandoned the use of Phase III trials, placebo controlled trials, because the concept of randomization and the concept of placebo was something impossible for them to communicate. They have tried. These are Western trained investigators. They have tried numerous occasions to do this. And for a physician investigator to say, "This is made by the flip of a coin, this is a randomized choice," is something that participants were unable to enroll in and the physicians felt very conflicted about that.

So they have regressed sort of in the sort of tools of clinical epidemiology, if you will, to Phase II trials because they feel it is unethical in large part to do Phase III randomized placebo controlled clinical trials. That was a common thought about that.

Now, in contrast, they spent a lot of time deliberating about -- in each case whether a placebo controlled trial was appropriate, whether randomization could be appropriate, whether they would get enrollment. We asked them what happens if people got enrolled in these trials. They said that, "Hmm, they usually just do not come back." That there was not trust in the investigator because if the investigator could not recommend one idea then they were not confident in coming back. They did not complain. They just went somewhere else. That was an interesting observation.

At the same time their emphasis on informed consent -- they thought that if they were going to get a consent for a clinical trial that it was the investigator's own responsibility. Investigators talked about their need personally to enroll someone using an informed consent process if a formal informed consent process was going to be used.

In several places, this is not surprise, the idea of a formal consent process seemed funny or unusual. The need to go through our usual heroics of forms and paper was somewhat surprising. They were willing to do

this but if they were going to do it, it required the investigator herself to go ahead and do that.

They thought that the exposure to U.S. research standards and regulation influenced their local standards. Clearly in each place we played a big role. Now whether that is because we came in with the golden rule and we had the gold and so here play by our rules, it is unclear how much they were saying that because we were there and visiting. "Oh, we like your rules." Versus the rules really did have an effect. But places did construct the research ethics committees or IRB's in a manner similar to the rules and also asked to have copies of rules.

We gave out copies of 45CFR46 and they thought this was wonderful because they never saw the actual regulations in practice. They are expected to abide by them but they came in with protocols that had already been handed down and worked over but they really enjoyed going over them.

The investigator who went down to Chile described a long discussion. He was getting ready to finish his discussion at noon and they insisted that they

all go to lunch and continue this conversation where he explained 45CFR46, which went on for about six or seven more hours. So they were anxious to learn about this material. They were not resistant to it but there were some questions that came up.

Other recommendations involved arguments related to justice. "Why don't you do things that matter to us? We are happy to help other people. We are happy to help with your problems." There is this notion of altruism but their claims about justice were such that "Please do some -- take care of some problems that matter to us." We heard that.

They wanted training, extensive training, done so that there would not be conflict because they really like this idea of compromise.

Well, those are the very preliminary results. We are anxious to meet with the other travelers, get them going on these site visit guidelines, see what we learn as we go around together, and then we are going to haul everybody who has gone on one of these site visits together and have an equivalent of a focus group because we learned when the three of us came back from our

respective trips that we remembered more of the details by having a conversation together and we are going to try and repeat that at the end of this before we provide sort of more final results to you.

That is the overview of the project. I would be happy to sort of describe any of that in more detail.

DR. MESLIN: I think we will hold off on questions until Dr. Kass gives her presentation.

Thanks, Jeremy. Thanks very much.

NANCY KASS, Sc.D., JOHNS HOPKINS

DR. KASS: Thank you and thanks for inviting me. It is a treat to be here.

What I would like to do briefly is tell you about the contract that I have with NBAC and then similarly would be happy to answer any questions.

The purpose of the study that I am going to be conducting with the help of others is to find out what United States based investigators who conduct work in the developing world think about their having to follow the U.S. human subjects regulations, what their experiences have been with that, and what their opinions and attitudes are about that.

We are going about that using two different kinds of very traditional empirical methods. One is qualitative and one is quantitative.

For the qualitative method we are going to be doing five focus groups with U.S. based investigators. Two of those will be with academically based researchers. Two will be with researchers who work in the private world, private industry. And one will be with federal government employee researchers, CDC, NIH, et cetera. We have thus far done one small focus group. I will tell you in a minute why we have not done more and I will later show you some findings from that first focus group.

We then will do a mailed survey to American researchers across the country trying to target similar kinds of people, that is a lot of academics, some government people, some private industry researchers.

I will tell you that we have distributed to you a very, very, very draft version of our survey because using as an excuse today's meeting we are giving you a version that is in an earlier draft form than I otherwise would have given to your committee but if anyone does have comments it is in certain ways the perfect time for us to

get some feedback.

I will talk you through the sections of both the focus group and the survey to give you a sense of the kinds of things that I have understood from Eric we should be asking that NBAC is interested in but, obviously, please let me know if there are other kinds of things and certainly when you look at the survey in the future.

We ask people a lot of questions about the IRB experience, both in the United States and in country, and what it has been like from their perspective, which includes very objective factual questions like "how long did it take to get through; how many back and forth submissions were there?" Again, for all these questions there is a parallel question both for U.S. IRB and for in country IRB. We asked a lot of questions about, "Were any of the following issues raised by your IRB," trying to get at things that I think of as sort of more content fundamental ethics issues as well as administrative issues.

So, "Did the IRB ever ask you about sample size? Did the IRB ever ask you why you are doing the research in this setting? Did the IRB ever ask you if

research could be done in the United States?" And then similarly, "Did the IRB ever ask you to change the consent form," and various things like that.

We asked then a large section of questions about consent asking both for the investigator to list all the various methods of consent they might have used, whether their IRB ever gave them any difficulty with trying to use nonwritten methods of consent if that was relevant for them. We also asked them which methods of consent they thought were most effective in achieving understanding and again a lot of other opinion/attitude questions about consent.

We then asked questions that are specifically about rules and guidelines. Not exclusively U.S. rules and guidelines but predominantly.

And then a series of other questions that we sort of called general ethics kinds of questions which touch more on issues of justice.

We have -- just to let you know because I imagine everyone does not know the -- for your benefit you do not know ordinarily what procedural requirements exist for someone like me in wanting to do this kind of survey

on behalf of NBAC.

OMB, the Office of Management and Budget, has a law called the Paper Reduction Act, which means that I cannot burden Americans with paper, of sending out a survey, which obviously in certain ways is very appropriate. It does, however, mean -- and I just tell you this in terms of understanding the time line -- that from the time when Eric and I first agreed that this work would go forward to when we can send out a survey is going to be about six months, and we are probably four months into that process, which is the good news, and it means that we can start sending things out about two months from now.

Obviously we have plenty to do. We are working on the survey and we are getting our sample together.

Those rules -- I will not go into the ways in which they do and do not apply to focus groups but we are able to do two small focus groups as the end of the situation about that. So we have done one small group so far.

Why don't -- if you would not mind turning

your chairs around and looking at the transparencies. I will just tell you I picked some very -- I picked some quotes from the first focus group that we did that I think are representative of the kinds of things that came up in that group, which is the only one I can say anything about. This was with academically based researchers.

(Slide.)

"I guess part of my frustration with this system is illustrated by the consent process. We are given these forms from the IRB which have a little stamp on the back and three pages. It says to contact so and so at the U.S. telephone number if you have any problems."

"If there were a menu like here are four or five acceptable ways of getting consent then people in a country could look at it and say, 'Well, I think for this country this is the best.' I think expecting some committee in some country to come up with their own approach probably is not realistic."

"One of the problems we have had is the lack of resources that exist in developing countries and undue expectations about putting together an IRB and where the resources will come from. Even to bring people for

meetings you have to take people out of their work and there is no compensation for them."

Actually let me say something about the last two comments because I think those themes came up over and over again. The first one about the need for flexibility, and I will talk more about that in a minute, and the second about the need for resources for in country IRB's. The situation is different than at least the way it works at Johns Hopkins and an ability for the IRB to function without resources.

(Slide.)

"When things go through the IRB here it is a very simplistic view of the whole consent procedure because we just write up what the individual is going to hear and, in fact, one does so much more. We do a lot more with the community education and discussion with community leaders. You sort of go all the way through the system and then the final thing is when you have this one on one interaction but there is all of this other stuff that surrounds it. I mean you say that in your application but that process does not really get captured."

This person was saying if it is not clear from here that all her IRB -- American IRB cares about is the individual consent and the individual consent form and her sense was that there were many, many steps that preceded that that really were the ones that contributed to the understanding of the participants.

(Slide.)

"I often feel that what we are providing to the IRB is a piece of paper that would protect them and that they could show the press or the ethics police that they obtained informed consent, that they did an ethical study that was reviewed, and that they put a stamp on the consent form and got lots of signatures so, of course, it was an ethical study."

I think part of what everyone here has been talking about is that maybe what we ought to do is move toward we should not be documenting consent but documenting understanding of the consent process. And maybe what would really protect the IRB as an institution and the funding agency is documentation that people participating in the study actually understand it so that having pieces of paper with thumb prints would be

insufficient but having some sort of evaluation.

There was some discussion -- I know this group knows that the U.S. regulations require not only an IRB review at the beginning of a project but annual reviews thereafter for the duration of the project, and that means that if you have an international project going on and an international IRB the in country IRB similarly needs to be reconvened once a year to make sure that the project is acceptable so this was a comment about that annual review process in country.

"There is no change in the consent form, why are you making me take these people who have other jobs come back together to meet specifically for your protocol. There is anger and then if there is no change they see that as inappropriate."

I think there is one more set.

(Slide.)

"In a lot of countries trained people are in short supply. They have a lot to do. They are all over committed even more than us."

"The concept of research may be unusual or unknown. In Swahili the word for research means 'looking

for something.' So when you say, 'Okay, we are doing research,' they say, 'Oh, what are you looking for? Maybe I can help you find it.'"

So let me just say a couple summary remarks about the kinds of things that we have heard and I guess I should preface that by saying -- well, let me say a couple of things about the summary -- the main things we have heard and I cannot sort of caveat it enough by saying this is one small focus group.

There definitely was the theme of flexibility and the need for regulations to be flexible. I will say as an editorial comment that many of the things that investigators said in the focus group they wish they can do, I am pretty sure from my knowledge of the regulations that they can do but they do not know that they can do. Things like, "I wish we did not have to get written informed consent." Well, the regulations currently allow that flexibility but on some level they were not aware of that flexibility and that, I think, is an important finding. So there were various issues raised about the need to be more flexible.

There were lots of issues that came up about

compensating local IRBs and that in many countries there is such a small pool of professionals that the IRB may be a national IRB so it has nothing to do with the institution where the individual works. People may have to travel to a different city. And to ask someone to take off a work day to go do this, particularly when there is no compensation, is something that was very difficult for people and sometimes mad them angry.

There also was some amount of findings, I would say, of the bigger issues. Some of the things that Jeremy alluded to about how research priorities get set but I am not going to venture into that territory because it was such a small sample.

One thing that I neglected to mention is that we similarly have had the input of many people in developing this and now look forward to your input as well, as well as having a team of people locally at Hopkins who are working with this on me. Joan Atkinson and Liza Dawson from Hopkins are here today, and some other Hopkins' ethics and international health faculty are involved in this.

I, similarly, will be sharing this with the

other NBAC international contractors, Jeremy and others.

And as a compliment to this -- I am just telling you this sort of as an FYI -- I have two other, unrelated to this, international ethics projects and for one of those projects we had the opportunity to bring together researchers from six developing countries and some American researchers for a big work shop in January. Dr. Keusch was there. And I have the transcript from those two pages of discussion and definitely some of the comments that researchers voiced in those found their way into the development of the survey as well.

So thank you.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: Thank you very much.

Let's just see if there are any questions that anyone has.

Bernie?

DR. LO: First, I want to thank Dr. Sugarman and Dr. Kass, both for coming and also for really taking a lead and doing these projects which promise to provide us with interesting and important information.

I had a question really that has to do with

the difficulties trying to get the information we want given the methodologies we have.

It seems to me that we are particularly interested in sort of focusing on concerns, problem areas, conflicts, inadequacies so that we can better get a sense of where there may be, for instance, unresolved issues and I am concerned about two things in our ability to find that out.

One is sort of the social desirability issue of doing this type of research. I guess, Jeremy, particularly with regard to going to a foreign country, you are sponsored by the U.S. Government, you are getting all the big shots in the country together, how do we get them to say, "Hey, you know, we have some problems here. I do not really want to talk about it too much to make us look bad or you look bad." So it is that kind of phenomenon. I think some of the things you brought up, "Well, they had never seen the U.S. federal regs before but they believe in them and follow them and love them and stuff."

I mean, if -- you know, is there any way in the design that we can sort of make it more likely we will

hear about issues that will be -- may well be difficult for people to talk about in a public setting with, you know, the other people there?

And a second issue is that we have seen in some of our other work, and you have certainly seen this in your work with the Radiation Commission, there may be discrepancies between the rules as they exist on paper and in IRB deliberations and what actually happens when you get down to a research project going out and enrolling patients and putting them in the trial and following them around. The perspective of people who are either in the trials or afflicted with the conditions which the studies are studying may have a very different perspective from the researchers or government officials. We have certainly heard a lot of information on that line when we did our previous report on persons of mental illness that may have impaired decision making capacity.

Is there any way of trying to get down to that level? I know you did that with your report for the Radiation Commission. It is obviously a lot harder to do in an international setting than in a U.S. setting but it seems to me that would be vital information if we could

get it.

It is just interesting as I hear you talk and sort of think about the newspaper investigative reporting reports that were done on some international trials, obviously very different goals, very different objectives and so forth, but they are very different pieces of the puzzle.

DR. SUGARMAN: Those are both really important points and both areas that we have spent some time considering.

In terms of the social desirability response there are several ways we are trying to go about minimizing the effects of the social desirability bias.

The first is that we are trying to build on established relationships that we have where there is a certain degree of trust so that the primary informant at each site is someone who has an established relationship either with Duke or with Family Health International so that they have had years of collaborative experience so as someone is coming in that there is more of an understanding that it is okay to respond. If we went over for the first day and said, "Hi, I am here from the

government. I want to help" kind of response and just walked in, we would be less likely to develop the kinds of trust necessary to tell stories which are somewhat difficult to tell.

The second thing we have done to minimize that is to frame things in a positive before we look for the conflict and the negative. And in our site visit guidelines what we ask for people to do is ask where there overlap, what are the things that they find beneficial, and then where do they find trouble.

The third thing we have attempted to do is let people tell us stories and to look for the stories in the research. For instance, we hear that the regs are much appreciated in the example that I gave you about the Phase III trials. They went through a whole set of discussions and deliberations and they went through the whole -- sort of almost as if they went through the literature on prerandomization as a departmental meeting. And so we heard them deliberate and labor about these regs. So we are finding some things where they say it just does not work.

We are trying to make them experts. We are

not the experts coming in with our rules and we try to emphasize that they are the experts on how research is conducted in their country and we are there to learn from them.

So those are the things we are trying to do. We are not saying, "These are our rules, do you like them?" Sometimes we get that response and we say, "Yes, we are glad you like them. And so tell us more."

And so it is usually not the first time we hear the story that we get. The information that we find is useful is the information that we get later on.

The anecdote I told you from Chile, the most useful information was how people then discussed these regulations in the context of this, "I am sharing my regulations with you. What happened at the result of a seven hour session about those regulations?" Well, there are a lot of stories that came up, "Well, that would not work and here is why" kind of stories.

The second issue about the roles of subjects, we have guidelines to talk with subjects if we can meet up with subjects. And that has been a bit more threatening for our key informant to sort of line up those

discussions.

The other thing is based on the work from the subject interview study for the Advisory Committee on Radiation Experiments we realized, you know, that we could get -- if we only spoke to one research subject we would worry about which research subject was selected. Are they picking sort of their favorite research subject? The one that knows the answers versus a more systematic sample.

So I think we have to take this study with the limitations in mind that it is a series of case studies at eight places. We are going to try to flush out in as greatest detail as we can about those places and how research is conducted. And should there be a need -- and I think there is a need but it is beyond the scope of this project -- to find generalizable data from the prospective research subjects, we will probably need to think through carefully the sampling frame for that.

DR. SHAPIRO: Okay.

Bernie, one more question.

DR. LO: If I could ask a follow-up question with regard to the second. Are there countries in which there are community-based organizations as there are in

the U.S. that represent potential research subjects or these people with the conditions which might be studied, advocacy groups, community groups, whatever, women's groups, labor groups that you could talk to?

DR. SUGARMAN: Certainly.

DR. LO: I just think anything we can get would be really useful obviously subject to the limitations of sample.

DR. SUGARMAN: Yes. I mean, there are -- if we get -- you know, we will be asking and looking for those sorts of groups and if we can try in our very limited period of time in each place to get that, we would.

The other piece is we are also learning that folks have been -- have added additional structures and mechanisms in place.

In Kenya, for instance, they were concerned that the normal mechanisms for AIDS research were not sufficient even with international funding and they developed and independent procedural mechanism for which to work on things. And then in addition to the formal structure there is an informal structure where the nurses

find out on the wards if the investigator has not followed the procedures they sort of will tell on them and ask to see the form before they will administer agent.

So there are a variety of things that are coming up and we are learning things despite the inherent limitations of an approach like this.

DR. SHAPIRO: Larry?

DR. MIIKE: First, just a comment on your selection of the countries and on what basis. I guess we can get that from the staff.

My understanding is that these countries were places where you already had working relationships and you built upon that. So is there any relationship to the significance or quantity or whatever measure of the American presence in relationship to the importance of the research in the countries you selected?

And then my second question is really the one I am most interested in, which is when you -- I assume that most of the kinds of research that is being conducted in these countries are clinical trials and they are multicenter international trials across large -- the kinds of things that Dave Cox is involved in. I am sorry that

Dave is not here because Dave would have been the perfect one to ask that.

In your looking at the consent process and the IRB process do you see any obvious conflicts between the aims of the U.S. researchers in these multicenter, multicountry trials and the adjustments that you have to make at each country level? In other words, the conflict between the ambitious theoretical design of the project and then what actually comes out at the end when you have got to deal with the reality of the individual country variations?

DR. SUGARMAN: Okay. The first question is a bit easier to answer so I will start with that.

The country selection was limited by a couple of things. We really wanted to strive for as much geographic balance as we could. Yes, FHI -- I sit on their IRB and so I know we have reviewed protocols for, I believe, up to 100 countries so we have sort of a wide selection of places to choose from.

We were limited in terms of when there were travelers going within the time constraints and within the budgetary constraints of the project. So we have sort of

a two-month interval to do these visits and we are trying -- as I said, we are piggy backing on so we are trying to always get a compromise between where there is variation that -- we suspect that there is going to be huge variation and even within a country there is going to be enormous variation as well.

The point here is to inform the conceptual debate and to tweak it. We are not going to be able to say that this is research in the world at the end of this project. This is not all the problems but I think -- I walked away even from these visits so far having learned an incredible amount that sort of changed what the priorities are for possibly adjusting regulations, modifying regulations, what priorities were to people working in the field, and I think these case studies can be used in that way.

Certainly there can be other studies to look at these questions of generalizability later.

So mostly logistical, financial, the usual things that in some ways work on that. That is how we made those decisions.

And we are continuing to refine it as people's

trips change and if we learn more.

The second question about informed consent and, yes, I think the folks that we have been involved with have been involved in a series of -- sometimes they are clinical trials, some are prevention trials because they are prevention and some are STD like prevalence trials because of the work that Family Health International does. Some are oncology trials. The hospital that was our primary respondent in Taiwan is a national cancer hospital.

So informed consent raises a lot of interesting issues and I think we -- Patty Marshall's almost entire project is on informed consent and I think we will have to wait to see what Patty learns. Patty will be using our site visit guidelines in a trip to Nigeria where she is going to focus on these consent issues.

But, in addition, we found some interesting things already. We were concerned of how you might get consent for an oncology trial in Taiwan if the nature of discussing cancer might be limited because there can be in some parts of Taiwanese culture hesitation to discuss the word "cancer" so how do you get someone to enroll in a

study on cancer if you are not using the word "cancer."

And so I focused a lot of my questions about that and it seems that, you know, some of our lessons learned are not quite true. They are discussions about cancer. Family consent plays a role in an interesting way that is difficult, I think, to sort of apprehend in a paragraph here. But the family -- the entire family is engaged in this project of caring and part of caring involves decisions about research as well. And so the idea that you would ask the patient first would be foreign to the patient, the potential subject, as it is to the family members if you ask first because it just does not fit.

So we raised questions about truth telling and informed consent and questions about family, individual versus a more community-based consent. Not in sort of the village idea but in the family as a whole.

That is where we are right now. I want to hold off giving you more information about consent. I think we ar going to learn a whole lot more as we go to these other sites. It is an incredibly important area.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Well, first, thank you both. This is wonderfully interesting stuff and very hard to do.

On that last point, Jeremy, before I ask my question I have just a brief comment about the truth telling because the standard of medical practice as the backdrop against which you are designing research and it really is very different. I am more familiar with Latin America and the degree to which family decision making is the model and truth telling is not the norm.

I will tell you, though, in Cuba what was very interesting is that after working with a large collection of health professionals for a while about this question, we then asked them as individuals whether if they were the one who were sick they would want the family to be told the truth and they would want, in fact, to be able to make the decisions. And, of course, to a person they all said, "Yes." So that the attitudes are even more complex than you are hearing because people will often speak about the country even if they are members of that country in these kinds of gross generalizations that belie a kind of ambivalence about attitude.

With that aside, two questions if I may, both

brief.

The first is what, if anything, have you learned in a plenary fashion about what is working as opposed to what is not working because stories of exemplary practice or stories of success can also be quite helpful?

And, second, what you have been describing so far are what I would call the ER level of ethical dilemmas. It is the ethical dilemmas that arise from small practices. In ER it is like the medical students and people mistaking them for doctors. It is all very routine stuff and very illuminating. But one of the things that drove us into this area is the Chicago Hope level of ethical dilemmas. It is the big ticket, baboon transplant problems. It is the you are going to give us different levels of standard care than would be present in the United States as a comparison against some new therapy or against placebo.

I was wondering how much you are picking up on what we perceive to be the driving force in some ways behind the project, which were these big ticket ethical dilemmas that hit the pages of the major medical journals.

PROFESSOR CAPRON: Alta, I have to say you sound like the commissioner from Los Angeles.

(Laughter.)

DR. SUGARMAN: In terms of the what is working, I think the notion of prospective review is probably working and it is modified in important ways to fit the country's needs but there are elaborate mechanisms of prospective review which I think is probably that pause before action. It may involve -- you know, that -- the time for deliberation and careful consideration of what the issues are, the logistical, practical, ethical issues that might be encountered in a particular project is probably important.

The idea that there is some formal process I think is working. The notion that you have to entertain the idea of consent, whether or not it is dismissed or modified or changed in certain ways, is at least entertained and understood to be an important process.

Beneficence is huge and we heard that at each of the places that really a risk/benefit calculus is done in a careful way. People cared deeply about protecting the interests. They do not want to harm people. Whether

or not they share the same notion of wronging is a sort of separate question. They focus a lot on not harming.

And I think what we are finding out is are -- is there now sort of commensurate change in about wronging people and sort of rights and trespassing other moral obligations. That is all I can tell you so far on that.

In terms of which TV analogy to pick I am not quite sure. We are trying to listen. We are trying to listen for little problems, for ER problems and Chicago Hope problems, and we are just trying to open up our inquiry as much as possible much like, I think, Nancy and her focus groups. Those are spectacular data. I cannot wait to see, you know, once the clearance comes through and we can be able to see how this generalizes in other issues because I think using these sorts of techniques when there are almost no data to drive empirical data regarding international research ethics except when things go bad.

I think this is our beginning to learn how to explore these things and qualitative techniques and ethnographic techniques, the kinds of things we are employing here are the most appropriate methods, I

believe, until we learn how to ask these questions. And this is something that people all over are struggling with.

DR. SHAPIRO: Trish?

DR. BACKLAR: I think that Dr. Kass was going to respond to Alta. Were you going to?

DR. KASS: Thank you.

I am looking at Eric to find out if it is okay that I mention briefly Adenon's proposal.

DR. MESLIN: Yes.

DR. KASS: Thank you.

There is another person who is a contractee with NBAC who has proposed a project that I think may answer some of the concerns that both Dr. Lo and Alta mentioned.

Adnan Hyder is a Pakistani physician who then has Ph.D. training in this country who is very interested in ethics and he would like to do essentially the in country complement to the project that I am doing. He would like to adapt the survey that we are working on to be relevant to developing country researchers and scientists and send this broad based survey to them.

So I do not know whether that will ease the social desirability but there is some hope that if you answer something anonymously with a piece of paper you might be a little bit -- you might say some things that you might not say to the visiting American guest. And, similarly, it will be a little bit more broad based from a larger sample that is picked a little bit more sort of randomly so that may address some of that.

DR. SHAPIRO: Trish?

DR. BACKLAR: Thank you very much for, Dr. Kass and Dr. Sugarman.

I am interested in something that you were talking about, Dr. Sugarman, and your experience of working with groups and families and obtaining consent in this manner in these countries because it is something of great interest to us here as we are working on our human biological material report.

I am wondering if you can give us some suggestions and ideas so that we could learn something from what you are learning in these countries and if you have thought about doing some work in this area to bring back information for us.

DR. SUGARMAN: We are beginning -- is this on?

DR. BACKLAR: No.

DR. SHAPIRO: Turn it on.

DR. SUGARMAN: Now? Okay.

I think we are beginning to find out some information about these areas about say family consent and how it is played out both in the trip to Chile or all three trips, Chile, Kenya and Taiwan so far. The study is not designed to look in a systematic way just about family consent issues and how to sort of -- you know, I would design a different sort of project to look specifically at that question.

I realize that there is a degree of overlap between these kind of problems and work we are thinking through at Duke in terms of genetic studies, stored biological tissues, and the need for some better understanding about family consent is clearly there.

There are few empirical data to inform that deliberation as well especially as it -- not only what we can learn from other countries who have been doing this and continue to do this despite our notion of the individual. So we can, I think, learn -- you are right --

from the experiences of folks who have continued to engage in family decision making when we have focused on individual decision making.

But also what that means in the United States and how one balances individual consent versus family consent.

As an aside, we have a study, a randomized trial of two approaches to obtaining informed consent for BRCA1/BRCA2 testing at Duke and the notion of consent -- giving consent to participate in that trial in some ways means you are giving consent for your relatives and yet we have been finding -- and again we did not know enough to design the study to look at the questions and the sort of issues that have come up where there are family disagreements and agreements about the participation of a patient or subject on trial.

And by virtue of giving consent a woman who is eligible for this trial has to have a family risk of breast cancer and has to -- and in that way is enrolling her family, whether or not she has spoken with her family about these issues or not. And so we have built in a series of protections but again I think we would have to

design a different study to answer that completely but we may learn something.

DR. SHAPIRO: Thank you.

Diane?

DR. SCOTT-JONES: I have a question that is somewhat similar to that. It has to do not just with consent but with the understanding of the research enterprise itself and I recognize that there are some difficulties here in the United States with what people understand they are participating in when they agree to be in a study but you also have language barriers that you mentioned with the example from Swahili and I would just like to hear a little bit more about your thoughts about what researchers can do to address the issue of the public understanding of the concept of research.

DR. KASS: Maybe we will both take a stab at that.

You are actually right that this is something that happens in the United States as well, and as a matter of fact Jeremy and I are working together on another grant that is looking at that issue in the United States so you are absolutely right and it is a big problem with research

and it is -- you know, I -- at the beginning of this whole initiative we had a conference call with Alex and he was talking about -- I hope I paraphrase you right -- sort of the little issues and the big issues.

And a lot of what comes up in terms of tweaking the guidelines and making the rules more flexible and allowing people to use not written forms of consent are what I think are sort of the easy things. It is easy to change those kinds of regulations. We can make sure people appreciate that flexibility and proving understanding is much harder.

All I can say is that at least in our survey we will try to get a sense, and the caveat is that by the time I am talking to people it is perhaps third hand, of their sense of what kinds of things people understood and what kinds of things people did not understand, and if they implemented any mechanisms where at least their goal was to improve understanding.

Were they thinking part of what I need to do here is to try to get people to understand concepts that may be difficult for them or foreign to them like placebos or research just as a notion.

Whether it was helpful to use peer advocates? Whether it was useful to have quizzes?

I mean, there are certain kinds of tools that we have heard that people have implemented and I do not know the degree to which we will be able to hear that those things actually were effective.

DR. SUGARMAN: I think, I wanted -- Nancy mentioned some other work we are doing and I think we have a -- face similar challenges in the United States communicating what the process of research should be about.

One of the things that we learned -- the same example I gave you about this notion of placebos and randomization -- we sort of adhere to this notion that we need to privilege the level of evidence of a placebo controlled itemized clinical trial and at that we do -- in some ways -- allow a certain degree of therapeutic misconception on the -- and sort of also what I have termed recently a therapeutic paradox permissibility.

In some cases we sort of say that there -- Phase I studies, for instance, or early phase clinical trials are designed merely to test toxicity but at the

same time we expect -- you know, investigators use terms that suggest that investigational treatments have some therapeutic benefit.

When research subjects hold the idea that this therapeutic intervention holds some therapeutic intervention as well, we talk about that and how to minimize that in the informed consent process and, you know, we are working on ways to try to improve that here.

In other countries their integrity is such that they say, "We cannot do that. It is too big of a barrier. We cannot enroll patients in that kind of a trial because we will never be able to communicate that this research or investigational intervention is simply that. We cannot communicate it. We do not know how."

So they have sort of abandoned that form of research becasue of the way -- you know, and our approach is to say, "We will fix the informed consent process."

So I think we can learn a lot from here and we may also learn something about which types of studies are we going to do or are we going to really adhere to this idea that things have this therapeutic paradox.

DR. KASS: May I say one more thing?

DR. SHAPIRO: Yes.

DR. KASS: I also think it raises a question which I think as a researcher and an ethicist we never want to address, which is do we really feel like we have to have understanding to do research. I think we all say that we do but I also think that we all know that research goes on all the time where participants do not understand. And I think a question that we never want to face is whether the importance of the problem is so great that certain kinds of misunderstandings are acceptable.

I am not suggesting that the answer to that question is yes but I think it is a very important question and it is going to be relevant to the international context.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I would just like to follow-up. I would love to discuss this more with you at some other time but it just seems to me that in my own research often the people are going on their faith in me and others on the research team that we are not going to do bad things and I get back -- I do research as a developmental psychologist and recently in our study from maybe 300

parental permissions we got back two that said, "Thank you but my child is already in therapy." They have absolutely no understanding of what research is and they are just going on the trust in the researcher in the institution, not in real informed consent.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, you had very interesting presentations and I want to point out that it has taken the United States almost 50 years for the placebo controlled trial to be accepted much less understood. Almost 50 years by investigators, never mind by subjects in those trials. So that the process of coming to believe that that is really the right thing to do is not something that took a very short time.

I am particularly interested in an issue raised in one of your last comments, Dr. Sugarman, about the business of beneficence and harm -- of wrong. Beneficence and harm -- harm and wrong. I do not think that the dialectic of harm and wrong is finished in the United States is finished either. So I am sort of interested in whether when you come back you will have some sense of how a particular culture protects its

subjects. Sees the need to protect a subject and how, in fact, it does that. The elaborate system that we have laid out is a system to protect human subjects as well as to produce research that has valid results.

I do not believe it is the only way to protect human subjects and so I am interested in how other people see the protection of human subjects, not just whether they are able to comply with American regulations, which I call at other times a kind of ethical imperialism, because that is what is crucial if there is going to be real meaningful research rather than pleasing us but doing what is going on at a local level.

So I am interested in when you come back will you have a sense that in this country or this country or this country this is how human subjects are protected?

DR. SUGARMAN: I do not know what I will have when I come back. I would hope to be able to inform that.

DR. CASSELL: How about changing -- okay. I will take that. I take it is research you are doing so, of course, you cannot tell what the results will be.

DR. SUGARMAN: I cannot tell you if I will have the answer to those questions but I think we will --

we are and intend to focus on those issues about how -- the notion of how people are protected from harms as well as wrongs. And that is, you know, a tough area to get at in brief visits but we are obviously attuned to that issue of how folks are being protected.

DR. CASSELL: I am not sure that you understand what I mean. I do not think necessarily that being protected against being wronged is better than being protected against being harmed. They are two different value structures. I am interested in the protection of human subjects, not whether they -- you know what I mean?

DR. SUGARMAN: Absolutely. No, I see there are reasons to protect against both so I do not think we disagree on that area at all.

DR. KASS: I just want to also mention that in the other related work that we have been doing, which is more developing country based rather than U.S. based, a related issue that has come up is a community or entire country being or feeling wronged. Again it gets back to all these justice issues but the notion of "Why have you picked HIV to study in my country when measles is the more relevant issue?" Things like that. "Why is it that you

are studying something that we think is more relevant for the United States." It leads to very strong feelings of perhaps a whole country being wronged.

DR. SUGARMAN: One other point I wanted to emphasize is even though we are going to eight countries, what I do not want to come back and say is that country X does this well, country Y does this poorly. I think we need to learn from them. They are opening themselves up to answering some tough questions and to work with us. And that notion of them being the experts in how they protect subjects is the way I like to think through that mostly and to make sure that in the end we did not conclude that this country was a bad country and this country was a good country.

DR. SHAPIRO: Alta and then Larry.

PROFESSOR CHARO: I would like to put in a request, if I may, for you to keep your ears open for certain things. I know that your methodology has been already set up.

One of the recurring themes here, and in the comments that you put up there, is that certain aspects of the regulations simply do not function and they are

superfluous or counterproductive. An example might be the signed consent form.

Of course, regulations are designed with multiple purposes in mind. One of them is substantive to further a particular ethical agenda. But others are really much more bureaucratic and are not as apparent to the investigator or to the subject. For example, the need for some kind of evidence of what happened in case -- so that you can have monitoring and, secondarily, to have evidence that is standardized to make that audit easier.

Those are bureaucratic purposes and one of the things that is very important when people complain about the flexibility problems and counter productivity problems is if we can listen for alternatives that actually will still address the bureaucratic needs, which are legitimate but are often not apparent to the people who are being frustrated in their substantive endeavor that would be terribly helpful because it makes it much easier to imagine on a pragmatic level some actual alternatives.

And within that the second request is if you can to pay special attention to the ways in which these issues arise in noninvasive versus invasive research. One

of the recurrent things we have heard here in a domestic context, and it has spilled over into the international context, is that many of these bureaucratic imperatives that drive the regulations are particularly mismatched to noninvasive research.

We have heard from people who do survey research over and over that they are unhappy with the way the regulations operate and I would welcome any input that comes from the international scene that might help us to understand what might or might not be done in the U.S. context as well.

DR. SHAPIRO: Larry?

DR. MIIKE: One comment, Dr. Sugarman, that you made sort of perked my ears up and I wonder in doing your studies that you can maybe not reach a conclusion about an application, and that was the issue about in some of these countries, and I do not know how prevalent this is in your experience, is that it is very hard to do nontherapeutic research because of the understanding.

To me that is a big question -- a big issue, issue, in the sense that all the focus is on how we use these other countries. But if you turn that around and

say that if that is so in those countries then it is our citizens who have to undergo the nontherapeutic research before we can move on to the therapeutic research in those countries so it is not simply a one-way street.

Or that our residents are being used to further the benefit in those countries because if they are not allowed to do nontherapeutic research in those areas we can never move on to the therapeutic side until we do those first preliminary studies.

So that was one of the issues that perked my ears up just in terms of the kinds of interesting questions that may arise but which you may not reach a conclusion.

DR. SUGARMAN: I think this goes back to a point that Dr. Scott-Jones made earlier about, you know, education about research and what the -- you know, there is a give and take and I think the -- what we have found so far is the investigators, although they may not know sort of the chapter and verse of the regulations, they sort of understand the point of research, they understand the point of the regulations, the overall driving force like they understand research.

Their troubles are similar to the troubles that we have as investigators in the United States communicating our research to patient subjects. So we may stand to learn an awful lot about where -- what the -- what is the background conditions, not only the health care background conditions but also the social conditions that make communicating this process somewhat transparent and then also how we can do that abroad and how we can do that here and why it might be important to participate.

We did find that there is sort of a sense of altruism not only for other countries were willing to contribute to U.S. research. They also wanted to focus on problems which matter to them. So we heard that, "Yes, we are willing to help you out and answer your questions. We understand that the disease prevalence is greater here than the United States but could you also help us work on these other problems." So I think there is a lot of room there and we can -- you know, it is important how this is framed in lots of ways.

To Alta's point about the regulations I think there are two parts to that, which I would like to try to grapple with. One, it is sort of following Faden and

Beauchamp on the history and theory of informed consent where they lay out sense one and sense two and sense one is sort of the ethical approach to informed consent, the kinds of broad issues, and sense two is the bureaucratic rules which are in place for a variety of reasons.

The example you gave was one where they are sort of following sense one but missing sense two. They are sort of following it. They are taking care of folks but they are not filling out the forms. The reverse, which we would want also to try to identify, is if they are following sense two and filling out all the forms but not meeting sense one.

And so it raises -- you know, these are tough things to grapple with and we will get as much data as we can but again there are going to be eight case studies and we are going to do as much as we can and we hope that we raise as many questions as we answer at the end of it.

DR. SHAPIRO: Thank you. Thank you very much.

I have a comment -- I guess one or two comments and a very, very simple question. First of all, with respect to some of your work, Dr. Sugarman, I am really very pleased to hear or at least I thought I heard

your own sensitivity to I think what you have termed "ethnographic" approach to the work you are doing, which I think in my own judgment is exactly the right approach in dealing with cross cultural divides of the time that you are dealing with. So I really am very encouraged by that.

I think it is also probably true that what I call an informed not knowing approach is helpful not only in other countries but our own country where are experts in some things but not everything and so we are always in the not knowing situation whenever we are dealing with others who are not exactly like us. So I am very encouraged and think that will pay dividends in both cases in both of your work.

On the survey, I was particularly interested in what I could tell by a quick glance on sections D, E and F, which I think might really elicit some very interesting at least hints regarding that. I have not had a chance, of course, to review this with any great care but I do think that it is very helpful. I had not expected to see that in a survey and I think that is very helpful and a very kind of imaginative way to go about it.

My simple question is, two, how many people do

you expect to administer this to and, one, have you -- you have probably had to tell OMB how long it takes to fill this out or something like that in order to get whatever approvals are necessary. Do you have any sense of either of those two simple questions?

DR. KASS: I will give you a sense.

DR. SHAPIRO: Yes.

DR. KASS: We are still not exactly clear how many researchers there are in this country who work in developing countries. We are hoping that we will have -- that we will send it to a few hundred people and get back -- I am -- I will be conservative and say 100 responses. I hope it will be more than that. And what you see, I think, is a draft that is too long because that is how you always write a questionnaire. You put in everything you want and then you try to whittle it back. We would like it to be no more than 20 minutes to fill it out.

DR. SHAPIRO: I only really asked that question because as someone who gets lots of surveys across my desk the first thing you do is look at the lengths and then you look at the subjects and then you decide what you are going to do with this and you may not

make the first cut. It is too long so it might not even come up.

DR. KASS: Yes, point well taken. Yes, thank you. Good point.

DR. SHAPIRO: Okay.

PROFESSOR CAPRON: The question is always which vice-president to send it to.

(Laughter.)

DR. SHAPIRO: Any other questions?

Well, thank you very much. I very much appreciate you coming here today. We look forward to the work that you do on our behalf and, of course, the broader work that you do. Thank you very much.

DR. MESLIN: Thanks again. I thought we would perhaps invite Dr. Keusch to maybe give us a couple of remarks to give us an update on what the Fogarty International Center is doing in the area of bioethics research.

DR. KEUSCH: Shall I come up?

DR. MESLIN: Wherever is convenient.

DR. SHAPIRO: Why don't you just sit -- it is not quite a hearing but it is a -- there is a microphone

there at least.

DR. KEUSCH: Well, thank you very much for the opportunity to say a few words.

I can say that, like you, I think we have lots of questions and not many answers yet. Mr. Robert Eiss, who runs our Science Policy and Analysis Unit at the Fogarty Center, is with me and perhaps might want to amplify on some of the things I say because we have been working together on this.

The role of the NIH is, of course, to generate research results and within the NIH the Fogarty International Center is the only part of the NIH that has as its brief international research. Fogarty has been very much involved in capacity building for research and we see it as part of the role of the NIH to be able to partner internationally. I think increasingly international research is necessary to meet our own biomedical research needs and it has to be done in a mutually beneficial manner.

We see that as critically dependent upon the development of research capability, human capability, as well as institutional capacity and instrumentation and

research methodologies.

So as we look at the way the NIH works, which is predominantly through the extramural program and support to U.S. universities it means that partnering and network development is the way to conduct mutually beneficial research.

As we approach the new century we have said that there are several absolutely essential elements that are part of the human capability that is necessarily for an ethical and an informative research process.

So those basics to me are information technology across a wide spectrum of the use of information, whether it be at the high end in looking at DNA sequencers and protein structure, there are some places in the developing world that actually have the capabilities to do that, or simply the ability to collect data, to clean it and use it to inform a question.

Secondly, clinical research methodology. If we are concerned about the future of clinical investigation in this country I think the issues in the developing world are even greater.

Third, as we approach the new century, the

issues of genetics and genomics, and the promise of this new information to inform us about both health and disease and how we may alter the expression of genes in varying environments since it is easier to do that than it is to alter the gene structure, maybe that will not be true in the near future.

And then as you look across that whole spectrum of involvement it cannot be done without ethical content and we are very concerned about the fact that in the controversies that came up in the last couple of years the developing world was not heard and it was not heard, in part, because the experts in this country who were passing judgment did not recognize the expertise that resided in the developing world.

So one of our fundamental plans for the future is to help to develop that research capability, that bioethical capability in developing countries so that when questions arise, and they will continue to arise, guidelines are only the beginning and not the end of the process, and that there is a cadre of individuals who have the training and expertise to speak for themselves.

I also have the feeling that this cannot be a

unicentric approach. It is not the American approach to international bioethics and our plans from the very outset are to make this multicentric in its training and then that raises lots of questions of how the heck do you do that so we are in the process of trying to think that through.

And then all of this in the context of establishing an ongoing dialogue about the issues that will continue to be raised by continuing research activities and that is why my feeling is that the guidelines are only a temporary look at cross section and time looking at issues.

We cannot anticipate all the issues that will come up but I think some of the things that Dr. Sugarman and Kass were talking about points out that is, in fact, the case.

So that is where our plans are. We are hoping to pull together a group of individuals from the recipient countries, the developing world, as well as experts in international research and ethics to begin to think about what are the needs, how we might go about it and I can tell you that it is trans-NIH. The rest of the institutes

who are interested in carrying out their research in an ethical and informed manner are very much interested in seeing that this process go forward.

Thank you.

DR. SHAPIRO: Thank you very much. I am very pleased that you could be here this morning.

Are there any questions that anyone has?

Yes, Bernie?

DR. LO: I want to thank you for your remarks and really applaud your commitment to building the infrastructure and paying particular attention to ethical issues. I wanted to ask you two brief questions.

First, I wonder if you could comment on Dr. Sugarman's observation or Dr. Kass' observation, I do not remember which, that even if there were a cadre of people in a developing country to participate in an IRB that coming to meetings is a tremendous burden on them, much more so than, for example, IRB members in my institution. I would like your thoughts on how that might be addressed.

Secondly, a related issue that I have been working on having to do with data safety monitoring boards for international clinical trials, again the same issues

of wanting to involve the developing country as meaningful partners and yet run into the same problems about the infrastructure and sort of bringing people together for an actual meeting which would be taking time away from their other responsibilities.

DR. KEUSCH: Well, I will go back to my first comment which is that I have questions and no answers but I think in respect to the questions that you raised my -- I have had 30 years of experience as a clinical investigator working in the international setting and one of the issues is that the research culture is under developed in developing countries. You cannot make a living being a clinical investigator and being a research and so all of the investigators are part-time and they are often doing private practice and doing many other things.

Even in countries that have experienced significant economic growth, Thailand is one example that I know very well because I have worked in Thailand for a long time, and the attempts to professionalize research in the universities and provide a salary for a research that means that they can devote full-time to it is not -- we have not been able to implement that.

So I think there are some structural impediments but as we look ahead to the promises that I think biomedical research can provide to these countries they need to see it. They need to buy into it and they need to create a professionalism in the research, academic and as part of that the ethics of doing it. So I think it is a process that will work itself out in mutual self-interest.

DR. SHAPIRO: Thank you.

Other comments or questions?

DR. KEUSCH: Thank you.

DR. SHAPIRO: Well, thank you. Thank you very much for being here. We look forward to working with you.

I am going to suggest that we take a ten minute break.

PROFESSOR CAPRON: Before we do -- this was --

DR. SHAPIRO: I am sorry. I apologize.

GENERAL DISCUSSION OF THE INTERNATIONAL PROJECT

PROFESSOR CAPRON: Well, I have been after Eric to keep this on our agenda, which is difficult because we are competing with projects which have been on our agenda even longer and where we have struggled with

the reports or things that have been recently given to us to do on a short time frame.

You will see from what we have that despite some suggestion that we might be able to make comments about what people in other countries think on X, Y, Z or whatever, we are not doing those kinds of studies that will provide either for individual countries, although there may be one exception, Dr. Hayden's work, a statement which would lead to much generalization.

In Nancy's work there is a quantitative base which I think would meet scientific standards, we hope, for making statements about the questions she is asking.

But otherwise we are doing much more qualitative things.

I hope we keep that in mind. It was an issue that came up in one of our previous reports where the temptation to generalize and to act as though we can make these generalizations because it is attractive to be able to say so will be there.

I would hope that outside of the meeting because we really do not have more time to devote to it now you would communicate either to Eric or to Harold or

to myself thoughts about what we want to get out of this project beyond the narrow focus on whether U.S. regulations are inadequate to the task that international researchers are being put to and, in particular, the kinds of things that were coming out today about the ways that looking at questions abroad illuminate questions that we have not dealt with well at home, whether it is a difficulty that even American researchers after 50 years have had with the notion of the randomized controlled placebo blinded trial or broader questions about the relationship between a scientific enterprise that is asking people to sacrifice their own time and perhaps their own well-being in the interest of science, and obligations of beneficence that underlie medical practice.

So I do hope that there will be some communication beyond what we are doing today, Mr. Chairman, because we are in a situation where otherwise I think we will come up on August or September and have to do something very quickly. Obviously if we have more time beyond this year the project could be brought to a fuller conclusion but I asked that this be on here and your own agendas as you think about what you have heard today.

DR. SHAPIRO: Thank you. That is a very helpful reminder. We all will think about it.

Let me ask one question. I do not know if I am asking it to the commissioners or to our experts who are here today.

There was some talk -- I guess, Dr. Sugarman, you brought up the point that there did not seem to be as much conflict or not as much conflict as one expected perhaps between U.S. guidelines and appropriate other guidelines in other countries but nevertheless it was not 100 percent overlap. That is there were maybe some guidelines there that did not exist here and vice versa.

Just as a general approach is it generally thought that the right thing to do there is to sort of add these things together making sure you fulfill all of them if you are a U.S. researcher or do you pick and choose or has anyone sort of given some coherent thought to how you -- one either should or how people actually do deal with that situation?

DR. SUGARMAN: It is messy and it is messy because there are a variety of different sets of guidelines and ethical beliefs that play a role in their

decision making and they are trying to negotiate among the beliefs they know about and the guidelines that they are having to work with and the reality of their clinical practice.

I think we will see how they actually negotiate that and make decisions but it is not an easy and simple process and it does not -- a simple answer does not, I think --

DR. SHAPIRO: Let me tell you what is on my mind since I may have articulated my question extremely poorly. I am trying to put myself in the position of a U.S. researcher who has certain guidelines that exist and to that person, let's say, they are perfectly acceptable to them when working here and he feels -- he or she feels that it is -- these things are important and would not want to work in any other way. And they go abroad and find very different guidelines.

It seems straightforward to me that that person would have to fulfill the guidelines they always believed in regardless of where they work and to believe otherwise means there is no such thing as human rights beyond what you happen to believe.

Are those issues that are discussed much? Do people struggle with them? Is there literature on this?

DR. SUGARMAN: Yes. There is actually a larger literature on ethical imperialism is how the -- is where -- the term that is usually used to refer to it.

DR. SHAPIRO: But I am concerned with a little different aspect if you do not mind me interrupting you.

DR. SUGARMAN: Okay.

DR. SHAPIRO: I am not worried about -- or I am not trying to ask you whether we are trying to impose our rules on someone else. I am trying to ask myself how that person will demand that he behaves or she behaves when abroad.

DR. SUGARMAN: Right.

DR. SHAPIRO: So it is just not a question of how some other person of another country behaves, how he or she behaves.

DR. SUGARMAN: Right. I am not aware of a detailed literature talking about -- empirical literature that describe how people reconcile these conflicts other than sort of the letters to the editor that follow a particular publication about ethical imperialism.

I can say, though, that -- and this is important. Folks wanted to work to understand. There are good stories here. And, you know, if we only read the New York Times and the Washington Post when there is one bad experiment or two bad experiments we are missing the picture. We do not have a sense of the denominator. And folks are willing to understand and negotiate that. They do not see it as conflictual as we tend to see it. The debate about ethical relativism or ethical imperialism. They see it as something that needs to be negotiated and compromised, which is new information.

And so I think folks are reasonable and the question is what happens to the U.S. investigator when she goes over with a set of moral rules that says, "I will always get written informed consent and I cannot possibly imagine doing this research without informed consent." What does she do? I do not think we have that information but the response has been let's work together to carry out this important project.

In that spirit I think we -- that is where we need to be looking as well. As Alta pointed out, you know, what are the good stories, where is this consensus,

and I think we are going to have to -- we will be listening for that and hope to be able to provide you with some more data.

DR. SHAPIRO: Okay. The last question, Trish.

DR. BACKLAR: Actually I was going to ask Alex because maybe I misheard you. Are you concerned that -- are you saying that the qualitative data you feel will not give us enough information? You are not pitting that against quantitative data. I was concerned about what you were saying.

PROFESSOR CAPRON: No, no. I think the qualitative data will be wonderful in itself and it may supply some generalizations about the kinds of phenomenon that are seen but I do not think we will come back saying the Taiwanese view on this is whatever and I do not think that is the intention of this research. I was just -- I heard a few people saying, well, questions which might lead them if the report does not say that to say, "Well, why didn't we have a conclusion about that," because that is not what we are doing. I just wanted to be clear.

DR. BACKLAR: I just did not want to hear you put down the --

PROFESSOR CAPRON: Oh, no, no, no.

DR. BACKLAR: -- qualitative data, which I think is very rich and enormously informative.

PROFESSOR CAPRON: Absolutely.

DR. BACKLAR: Okay.

DR. SHAPIRO: Thank you very much. Okay.

We will take our break now. Let's reassemble at 10:00 o'clock.

(Whereupon, at 9:40 a.m. a break was taken.)

DISCUSSION ON ISSUES BEFORE THE COMMISSION

DR. SHAPIRO: All right, colleagues. I would like to get this part of our meeting underway. I want to return our attention now to the HBM report which we had been working through the recommendations yesterday.

I will turn the chair over to Tom momentarily. I just want to apologize. I will have to leave the meeting for about five or ten minutes very shortly but I will return as quickly as possible.

Tom?

DR. MURRAY: Thank you, Harold. I am looking around the room and not all the commissioners are back yet but we will begin anyway.

As we were saying yesterday we had some difficulties with recommendations -- the set of recommendations comprising 38 and 39 of the draft chapter five from our report and can we quickly go back and revisit to see where we are with those five recommendations.

My goal is by lunch time to have run through the full set of recommendations so that we know where we are before the next step and that is going to require a lot of self-restraint on the part of myself and the part of my fellow commissioners.

We agreed, did we, on number seven?

DR. CASSELL: Yes.

DR. MURRAY: Yes. Where are --

PROFESSOR CHARO: We skipped eight.

DR. MURRAY: We had agreed on six, I believe, is that right?

DR. LO: Right.

DR. MURRAY: We did not talk about eight. Why don't we talk about eight right now.

(Slide.)

Would everyone please look at recommendation

number eight?

Bernie?

DR. LO: On number eight I have concerns about using the term "interim." From my background "interim" means results -- you are collecting data and before the end of the trial you sort of look at the data to make sure that you have not answered the question already. And it is an issue in clinical trials do you let the people in the trial know the interim results.

I do not know if what we are really talking about here is at the end of the study you have findings that you are comfortable enough to publish and present at meetings but you think need to be replicated, whose clinical significance is not clear and you do not feel comfortable giving them to patients on which to base patient care decision.

So I am just wondering if we can clarify what kind of findings are we talking about because I thought we were talking about at the end of the study they are conclusions as far as you are concerned but they need to be replicated and the clinical significance is uncertain.

PROFESSOR CHARO: I think it is an interesting

point, Bernie. I know when I read it I was comfortable with this because the interim findings problem was the one I had in mind when these were being drafted. Both seemed to be pertinent. But the real issue here is about the recontact.

The issue is about recontact or even first contact of people who are identifiable becasue it links and for whom the findings have some ambiguity but there is a feeling that one should possible err on the side of more information to people or their physicians so we might want to just redraft this to talk about findings at any stage.

I think yesterday we did touch this -- on another aspect of this. We did touch on it just briefly. However we reorganize it, it would not be inappropriate to find this in the original recommendations concerning protocol design since the goal here is to have this part and parcel of the original design.

Carol?

DR. GREIDER: I just want to raise one other question and that is the word "clinically significant." What about the possibility of people wanting to go back and recontact for research reasons? Do we want to include

that in there that it should be --

DR. MURRAY: No.

DR. GREIDER: No.

DR. MURRAY: That would be a different -- that is clearly not what is intended. Well, I am giving you my interpretation. That is not what is intended in this recommendation. This recommendation has to do, as I understand it, with recontacting an individual in a sense for their benefit becasue there is a belief that there may be information of relevance to that individual and/or their families.

Is that a fair assessment of the intent of it? Okay. So it is not when the researcher just wants more info, it is when there is something that --

DR. GREIDER: Do we have something to cover that other case?

DR. MURRAY: Well, we have to --

DR. BACKLAR: It seems to me if that is what you want you need to put that in there, something about the benefit of the subject.

DR. MURRAY: Okay. Are we clear on -- Steve, in a second. Are we clear on the sense of what we want in

this recommendation? This is not -- Bernie is not clear or we are not clear.

DR. LO: I am not clear.

DR. MURRAY: Okay. Let's continue the discussion.

Steve, and then Eric.

MR. HOLTZMAN: I think in Princeton we had a recommendation about recontact where we brought together the different cases and we said it was important to separate. So to remind us there were three different cases for recontact. The one Carol has just discussed, which is where as part of the research design you anticipate, for example, that you might wish to recontact.

The second is where you have a finding in the research that is directly, if you will, from the research and there is a question about whether or not -- and what are your plans for going back to subjects to tell them something that came from your research, of that nature.

The third is when there is a serendipity finding not directly related to the research and whether you wish to fill that in. For example, you collect a blood sample and as part of just your QC of that blood

sample -- you are not doing an infectious disease study -- you do an infectious disease test on and you find out there is something present. Okay. So they need to be separated and I think we agreed that we would separate them.

With respect to the specific recommendation I do not think we can read it and how we feel about it independent of two other things. Number one, there was information handed out to us yesterday about a suggested addition. An implication of what is written in this suggested insertion is that the only time there can be recontact with the -- let me call it clinical finding -- a research clinical finding is if, in fact, you are working with samples where there was consent. If there was waiver of consent by the IRB you cannot go back. All right.

Now we do have text here where the Reilly principles are articulated and they do not put that kind of limitation on them so that is a question whether we think this insertion ought be controlling and then the second point is that if you go and flip the page directly to recommendation 13 we say that persons should be offered the opportunity to indicate whether they would like to

receive any interim findings. All right. There are other approaches to this where you will say you are not going to offer the opportunity for -- to disclosure of interim findings.

So I would just -- without getting us off track, Tom, are we integrating our thinking on all of these things?

DR. MURRAY: I have on my list Eric, Carol, Bernie, Jim and Larry.

DR. CASSELL: I am now more confused than I was before. I just read this little insert that was provided that really bears on this also about interim research results may be provided to research subjects only when, and then there is three odd or at least one of them is an odd sentence, and then we have this next number eight which is just not clear at all.

DR. _____: It is the biotechnology industry calling again.

DR. MURRAY: Eric is otherwise occupied. We will let you come back if you need to.

Carol?

DR. GREIDER: I thought that Steve's summary

of the three different cases of possible recontact that apparently were discussed at Princeton when I was not there was very helpful and perhaps they could be linked together somehow because in the recommendations it would be nice to have that spelled out.

DR. MURRAY: I see a kind of organization which said questions arising in research design, had subset, recontact and then either two or three, and since one is research sort of intended for the benefit of research and then the other two are intended for the potential benefit of the person to be contacted.

MR. HOLTZMAN: Yes. I distinguished the two by the way because the general argument about the research finding is it is preliminary and it does not-- has not really risen to the level --

DR. MURRAY: Right.

MR. HOLTZMAN: -- but some of those QC test you may be doing are, in fact, definitive --

DR. MURRAY: Yes.

MR. HOLTZMAN: -- all right. And so, therefore, if you are not disclosing it is for a different set of reasons.

DR. MURRAY: Thank you, Steve, that is helpful and clarifying to those issues.

Bernie?

DR.LO: I want to follow-up on Steve's point about what is the clinical value of the information. The way it is now phrased I really have concerns about the possibility of clinically significant information and I think we need to -- I have questions about what the ethical basis of giving information that is only possibly clinically significant when in other settings the standard is higher or stricter. Steve's parsing out the cases really illustrates the difference between a finding that you know has clinical value and it is considered as such in a clinical setting versus something that may or may, depending on future work, have any clinical implications.

I am just concerned about setting standards that suggest that it is appropriate or it should be encouraged for researchers to pass all that information becasue I think that is a very, very debatable question.

DR. MURRAY: Eric, did you want to reclaim the --

DR. CASSELL: Yes. I just want to go back. I

am trying to distinguish here between the finding -- an incidental finding that the person had Suchagamuchi (?) fever and that is crucial that they know that because therapy at this point prevents an ultimate terrible turn into Republicanism.

(Laughter.)

DR. CASSELL: And that is one kind of clinical finding.

DR. SHAPIRO: You just wanted to see if we were listening, right?

DR. CASSELL: Right. That is one kind of clinical finding, the incidental finding or which harm would be done if the subject did not know that. The other is what Bernie is talking about, this business of questionable findings and their harm may come by revealing data in its early stage. So I do not think we have clarified at all what the recontacting is about, those levels of recontact.

DR. MURRAY: I am going to exercise a lot of self-restraint and keep my place in line which right now reads Jim, Larry, me and Alta.

DR. CHILDRESS: I am not sure I have anything

to add because it seems to me the direction that Steve proposed at least for distinguishing these and then followed up by others, including Carol, I think that is the way to go but then we have to decide within that what kind of latitude we are going to allow but at any rate I think they need to be put together in the research design and then we make our decisions and recommendations about what we would allow for recontact and for contact under each of those.

DR. MURRAY: Thank you.

Larry?

DR. MIIKE: I want to distinguish between the language of our recommendation and what we mean by it and I think a lot of our problem is we are trying to put too much stuff in the language of the recommendation so that we get sort of focused on one area and then people say, "Well, what about the other stuff?" And I think what we are trying to put over here is simply a checklist for researchers when they design something.

So one checklist is, hey, you should anticipate the possibility in your research design that you may have to contact the subjects for clinical

information so we should not get into whether it is interim findings or final findings and make a more general statement about the clinical aspects and deal with the recontact for research purposes in another place perhaps. And then the text will explain the difference between the various types of things that we thought.

So my spiel is it should be a general checklist and then the details can be described elsewhere in the text.

DR. MURRAY: My turn. I have a sense this is an extraordinarily gifted group that is capable of thinking of a remarkably prolific series of possibilities and I think we make a mistake when we indulge that entirely. Rather than trying to anticipate all possible implications that we are better of, as Larry just proposed, alerting the IRB and the investigators that this could be a problem, has occurred and may occurred in the future.

So alerting it and specifying something in the way of procedure whereby they can do that rather than trying to articulate in great detail exactly what sorts of decisions they ought to make. So at this point I find

myself favoring a modest strategy rather than again trying to follow through all implications.

DR. CASSELL: Then in designing protocols investigators should to the extent possible anticipate the need to contact subjects for investigational or clinical reasons arising from their data.

DR. MURRAY: We may want to distinguish the two. We may want to distinguish those recontacts that serve the investigator's interest.

DR. GREIDER: In language --

DR. MURRAY: Pardon.

DR. GREIDER: In language that follows.

DR. MURRAY: In language that follows. All right. Well, that is a possibility.

DR. CASSELL: We did not say that.

DR. MURRAY: Carol, maybe you should say that.

DR. GREIDER: I just said you put it in language that follows. You could have a very general recommendation and then a very short paragraph outlining the possible types in broad ways as Steve described them.

DR. MURRAY: That would work.

Alta?

PROFESSOR CHARO: I have no trouble with the more modest approach. I do find myself thinking the way Bernie often thinks in this case where examples might be helpful. For example, the paradigmatic case I had in mind that addresses Bernie's question about possibly clinical significant has to do with things like Apo-E and the kind of research that was revealing, an association between Apo-E and Alzheimer's that was weak enough that it was not clear that it is clinically significant and yet was substantial enough that there is room for disagreement about that and that early notice to people that they have this has a complicated cost benefit analysis in which benefits are not only the very few preventive strategies that exist but being alert to possible clinical trials in the future.

And interestingly enough, an area which kind of slops over, Steve, in blurring your categories because it is also recontact possibly in order to do this kind of tiered research that David Cox always talks about in wanting to then identify the subset and do further testing on them to further clarify the multifactorial nature of this disorder.

So if it would be possible even with a modest list to try to come up with these paradigmatic cases to illuminate these concerns this I would find helpful in communicating to investigators what they are supposed to be keeping in mind and why when you are working with separated materials that may have been taken from people many, many years ago it is particularly problematic that you are going to go back to them and suddenly tell them that they have possibly a trait that possibly might be connected to a disease that might possibly occur.

DR. MURRAY: Alta, would you be amenable to seeing that that gets incorporated in whatever chapter leading up to the recommendations discusses the issues? I do not think it belongs in chapter five if we are going to try to keep chapter five slim.

PROFESSOR CHARO: Well, I am not insisting that it be in chapter five. What I want to make sure is that the recommendations reflect this kind of problem. It may be that I have not read the chapters recently enough and that example may very well be in there and I apologize if it is.

DR. MURRAY: Steve, and Alex.

MR. HOLTZMAN: I have laid out three cases. I think the recontact for the research study is distinguishable from the other two. If we look on pages 29 and 30 we very simply and succinctly have laid out the different positions. Like the one says interim findings should never go back. Another says autonomy requires that all interim findings desired by the subject go back. And then there is a Reilly position which says you should lay out a plan which will involve the role of judgment. All right.

My personal feeling if I were -- I think the commission in its recommendation effectively is going to have to adopt one of those three kinds of positions on the go-back with findings, not the recontact for research purposes. And my personal belief is that I think that Phil Reilly probably has it right and that the kind of prescription he lays out, which is laid out here on page 30, is at least to me very attractive.

DR. MURRAY: Alex?

PROFESSOR CAPRON: I find myself in the position that Larry so often articulates of being frustrated and puzzled as to what we are doing here. I do

not understand that we have yet clarified the terminology that we are using, the difference between interim findings and findings that to the investigator would be published in the New England Journal suggesting that the investigator found something but had not yet stood the test of time. Particularly with many of these genetic association issues there is a finding of a gene which is associated with a disease but the question is, well, what is the clinical significance of that over the course of a lifetime. Versus the fact that although we often think of research standards being very high, a study that is being done using a research technique of finding a gene may not be up to clinical laboratory standards so it would not be a finding which a clinician would say even is ready to be communicated as a result about this person, an accurate -- I mean, just simply the accuracy of the result.

So I do not know what our intention here is. I think what Steve just said is closer to what we should be talking about, which is what are the limitations on situations in which it is permissible to go back and he drew attention before to this insert and the second bullet here, I think, as Eric said, is unclear in its meaning.

Only individuals who are prospectively consenting to participate in research using human biological materials can express their preference to have interim results provided to you but that has that problem of the interim results language.

But if this is a descriptive statement it is true. Only if you are asked can you express your wishes. And that tells you nothing. That is chronological. I suppose that in writing this thought was may -- it is only permissible to convey to such people these interim results and that we should at least, as Alta often suggests, presumptively with a strong presumption say if this is a study in which consent has been waived the presumption should not be -- you should be against clinical findings dropping out of the sky on you when you had no idea that someone was about to announce to you that you are in some high risk category when it was not something that you knew was going on.

That to me would be worthwhile saying. That may come out on the next page if we revise number 13 about the consent process or some other place. Perhaps Kathi or others who have worked on the report can say if I am

overlooking something. But I do not find number eight as it now stands useful at all and I would just assume not have it than have the language that is here.

I think the notion of having a statement that a research project to be approved should include a statement of what sorts of findings would trigger a plan to recontact and a description of how that plan will be carried out, including conveying the necessarily preliminary nature, not interim nature, not interim findings as that term is used, of the findings and the limitations of research results or something.

I mean, in other words, it is important for the investigator to have thought it through and that is really what the Reilly point is. I agree with Steve about that. And it is important that the IRB see that and approve it but as it stands now I would like to see eight dropped.

DR. MURRAY: Although I am a little confused, Alex, because -- and I have no -- I did not write eight as it stands here but I think that is exactly what it is attempting to since it tells investigators to think about it in advance and to say what their plans are. It tells

IRBs to make sure they attend to do that and to consider that in whether or not to approve a protocol.

PROFESSOR CAPRON: I do not find --

DR. MURRAY: Maybe you do not like the language at all.

PROFESSOR CAPRON: I do not like the language of it and I think that the language on page 30 is -- I mean, the language here says, "Anticipate the need to contact when interim findings suggest the possibility..." I mean that to me -- I do not know what that means.

DR. MIIKE: But that is why I am saying to make this a more general "in your checklist" and then we can adopt exclusively the criteria by, you know, suggesting criteria, which is on page 30.

DR. CASSELL: But doesn't enter into the calculus of risks in the first place? I mean, if that is such a risk could -- is part of the research then that is not minimal risk research anymore. Somebody could find out that they might have Alzheimer's and that is risk. And then consent should not have been waived in the first place.

PROFESSOR CAPRON: That goes to this

underlying question of if you have such a finding is there an ethical obligation to convey it or conversely is there an ethical obligation not to convey something which has all the qualifications that are inherent in any such research.

DR. MURRAY: I tried to put myself in the position of someone whose tissues are being used and say what would I find morally permissible, what would I find morally outrageous in the way of coming back to me, what would I find morally outrageous in the form of not coming back to me when you learn this. So the fever that --

DR. CASSELL: Well, Bernie whispered to me --

DR. MURRAY: -- Eric described earlier, you know, maybe I would think that would be a horribly outrageous thing for you not to come back to me and say, look, you should be taking antibiotics for this.

DR. CASSELL: Bernie described to me the situation where somebody calls me up to tell me that I have Suchagamuchi fever out of this research. I did not know I was in any research in the first place. And that is what the central problem is.

DR. MURRAY: Alta?

PROFESSOR CHARO: You know, I think I feel like we have enough to begin to redraft this. I do not take seriously the idea of dropping this because I think everybody agrees we would like to highlight that there are particular concerns about going back to people, particularly people who have no idea they have been involved in research specifically because the research was on excised tissue long taken.

I would just not want to encourage any thought about dropping this. Reformulating, find a new place, fine, checklists, informal, great.

DR. MURRAY: Can we take that as our marching orders in recommendation eight? It needs pretty substantial reformulation. The current form simply is not acceptable to us but that it should continue to exist as an instruction both to investigators to anticipate and plan for and for IRB's to include in their review?

PROFESSOR CAPRON: May I suggest an approach to that? Why don't we think of the recontact issue as deserving its own sort of set of recommendations and read through what is on 29 and 30 and sort of say having considered the points raised there what recommendations

would follow from that.

DR. MURRAY: I have no objection to that.

DR. SHAPIRO: I think that is necessary because as it stands now as Steve and perhaps others have pointed out the sides are presented without any real obvious conclusion to be made.

DR. MURRAY: Although it would be -- it might be adequate to just say it is a problem and investigators ought to think about it and IRBs ought to review it without us giving specific direction as to, you know, pointing them to a literature that exists about it without us instructing them as to how they must -- with substantive agreements they must reach. But maybe we want to comment about the substantive judgments. I do not want to, you know, preclude us from choosing either way.

What I would like to do is identify the people who are going to work at redrafting the set of recommendations pertaining to recontact and I have four candidates. Bernie, Carol, Steve and Alex. Is this a necessary and sufficient set of people to redraft that? What I will do is I will ask Eric, who I have already warned I am going to be doing this, to arrange for a

conference call, an exchange of drafts and a conference call where the four of you will settle on what the recommendations ought to be. Is that acceptable to the four? I realize this is a little more directive than we are accustomed to being but I want to --

PROFESSOR CHARO: Tom, just a point of order.

DR. MURRAY: Yes.

PROFESSOR CHARO: Before you hand out the assignments. Because there have been other places where there has been a suggestion that one might want to reorganize all of the recommendations I am finding myself reflecting on yesterday when I was taking on various assignments, one thing that is really possible since what is now a single recommendation may wind up being spliced into multiple places or several will be combined, and until the staff has actually had a chance to think about alternative organizations it may be difficult for us to be working on specific pieces.

As a matter of just a point of order I wonder if the staff has had a chance to work with you on a game plan for how to involve our assistance.

DR. MURRAY: There will be certain

recommendations where we have talked about maybe combining. In this case I think we can carve out the recontact issue and write a set of recommendations. There are two different tasks. One task is how to reorganize the chapter and I agree that the tasks are -- they are interrelated. Yet I think it is absolutely essential that we make progress and reach closure on this report and I know of no other way to do that than to involve the commissioners in committing themselves to particular forms of recommendations and that is what I am trying to push here, Alta.

So I really would like to see us do this where possible. Granted that some of the recommendations we may say, well, we cannot do number 43 alone, 43 ought to be recombined with two, fine. That group should rewrite them both. I have no problem with that.

DR. SHAPIRO: I could make a suggestion, Tom. I quite agree with you but I think it is not implausible when the staff initiates this call X days from now that they would have a concept of the kind of thinking about this as to how this would really fit in and so the call takes place in some kind of productive environment that

way.

DR. MURRAY: That would be fine, yes. Bernie and Steve have their hands up. Bernie?

DR. LO: Yes. Just as a procedural point is there anything to prevent that working group getting together at lunch to try and do this while we are all here. Trying to find a conference call time is going to be a little tough. Maybe we can just all get together at the break or something.

DR. MURRAY: That would be great. Maybe four people do not want to be involved. This is not -- one can dissent from my request that you participate in the drafting of these recommendations.

DR. SHAPIRO: But not easily.

DR. MURRAY: Not easily.

DR. LO: I think it is great you are being more direct --

DR. MURRAY: My South Philadelphia contacts will visit you but you can dissent and I certainly -- if you can do it at lunch today that would be terrific. Terrific.

Steve?

MR. HOLTZMAN: Well, I am actually with Harold because drafting is easy when you know what you are supposed to draft and to me at least the recontact issue with findings. Let's put aside for research purpose. To me it is actually very straightforward. All right. And the commission has to make certain decisions. First, we could take the position, which you articulated, that we say to all IRB's this is an important issue for you to be thinking about and every study should say whether or not you are going to do it and here is the literature, see page 29 and 30. It is up to you.

A second position says you may never recontact and that is our recommendation.

A third position says you may recontact, all right, and you will probably follow the Reilly kinds of things here, all right, that says, you know, you need to have a consideration as to how solid is the finding. All right. How important is it and is there anything you can do about it?

If you look at what Reilly says, the case of these Alzheimer's falls out, all right, but -- and this is the third part of the -- but if and only if there was

consent to the study. All right.

And then the fourth position is the same as the third except you say there does not have to have been consent for the study because the primary motivating force for the recontact has to do with prevention of harm and does not have to do with autonomy.

I think the commission has to decide which of those four positions we are taking. All right. And you write the recommendation.

PROFESSOR CAPRON: Steve, there is an additional one which is that there is a presumption there will be no recontact if the research plan has not set forth in advance a process of anticipation. That means that if a person comes back in and says something extraordinary has happened here and I want to recontact them. Let me explain I did not anticipate it. That sort of holds people's feet up to the fire a little bit.

Think your project through. What could you find that would be clinically useful enough that you would be going back to people and how are you going to build that into your consent process up front so you do not surprise people.

And when you have not done that I think the inclination is to say it is too late.

DR. MURRAY: Bernie?

DR. LO: To follow up on Steve's line of thinking, which I think is really right, it seems to me we all should be for the IRB asking investigators to think it through in advance. I think -- I personally think that using discretion tends to be the best answer to most questions and saying that you never can do it or always should do it, especially in this context, probably is not going to work.

I think Alta and Eric raised some other concerns about how this situation is unlike other research because you may not -- the subject may not have known he or she was in research and that has to be factored in explicitly.

I mean, can we -- can I suggest that we all say we should take Larry's suggestion as given and say you should use your discretion in weighing all these factors and thinking it through?

DR. MURRAY: That is a direction to the IRB, to the investigator or both?

DR. LO: Well, both. Presumably the IRB -- the investigator is to come up with a proposal that the IRB is going to review so it is both of them.

DR. MURRAY: Steve, do you feel like you have an adequate information on which to work on this draft or do you still feel like we need to have substantially more discussion about the --

MR. HOLTZMAN: Well, what is the sense of the commission?

PROFESSOR CAPRON: We need a straw poll.

DR. MURRAY: A straw poll would be fine. Let me make my pitch. Flexibility, permit discretion and flexibility as I think both Larry and Bernie have proposed, particularly when the issue is -- and here I am really talking actually exclusively about the question of when it is prevention of harm to the source of the materials.

Do we really want to be putting IRB's in the position or the investigators in a position where they do discover something which could prevent enormous harm to an individual but because they failed to anticipate it before they did the study they cannot tell. So the investigator

failing translates into a failure to prevent harm to a tissue source. That seems an unusual thing to require.

PROFESSOR CAPRON: Well, you know, we talk about discretion. We have reports saying IRB's do not do their jobs very well. I mean, so to say discretion -- what do we mean by discretion? We know researchers are inclined not to want to go through a lot of advanced thought on these things. If we have a rule that just says discretion what that means is --

DR. CASSELL: Do not do it.

PROFESSOR CAPRON: Hmm?

DR. CASSELL: Yes, do not do it.

PROFESSOR CAPRON: Does it?

DR. CASSELL: Investigators, they will not do it. I have discretion and I do not even want to bring it up.

PROFESSOR CAPRON: Do not bother me.

DR. CASSELL: Do not bother.

PROFESSOR CAPRON: And then we end up with results -- well, gee, I better contact these people. I have not thought it through. I have not told them this is --

DR. MIIKE: That is not what we are saying.

(Simultaneous discussion.)

PROFESSOR CAPRON: Excuse me. I am responding to Tom's comment which was --

DR. MIIKE: So I am but I am not -- that is not what we are saying and I do not think that is what Bob is saying. What Tom is saying is that IRB's and investigators must consider the question. Whether they decide to do anything about it or not is a separate issue and I do not think we can dictate all the examples and all the circumstances under which they should not consider it or develop a plan and that is what we are saying here.

PROFESSOR CAPRON: Okay. I understood Tom saying he thought it was extraordinary the notion that we would allow harm to occur because someone had not planned in advance.

DR. MURRAY: I was laying out a particular sort of set of moral intuitions that would pertain to the kind of prohibition on recontact which you propose as one of the possible actions we could take.

PROFESSOR CAPRON: Right.

DR. MURRAY: And I do not think that kind of

prohibition is wise.

PROFESSOR CAPRON: It is certainly true that someone in a research project could find something that no one anticipated of such urgency that you would have no problem convincing a reasonable group of people that this is one of those exceptions but we have to go -- people did not anticipate this, we did not warn people this was in the offing, and we found that there is this epidemic going on among these people. We have to go speak. No question.

But to talk about this as something in which we would create a presumption that you do not go back and contact people unless you have thought it through in advance well enough to have anticipated the kinds of things that you would find significant and have put that into the process in which you originally communicate with them so that in a situation where you have not communicated because you have asked for waived consent or where having communicated you did not mention that recontact was a prospect at all, the presumption would be against doing it then.

I think it is very easy to say, oh, these findings are very interesting and we ought to tell people

about them. I am just saying if the presumption suggests that you are going to have to have a very strong case.

DR. MURRAY: No problem.

PROFESSOR CAPRON: If you are going to have no problem with that then we are --

DR. MURRAY: Before it was framed in the language of an absolute prohibition.

PROFESSOR CAPRON: No, I said presumption.

DR. MURRAY: The language of presumption I have no problem with.

Steve?

MR. HOLTZMAN: If I were writing the recommendations --

DR. CASSELL: Which you will be.

MR. HOLTZMAN: -- I would --

DR. MURRAY: This is not a hypothetical.

MR. HOLTZMAN: -- I would turn your attention again to page 30 starting at line 10. All right. Which is the Reilly set of things, which effectively we recommend that IRB's or institutions develop general policies taking into account these things and that they require in the submission of the proposal answers to the

kinds of questions. All right. This starts to get to Alex's point. Now the assumption is people are going to be addressing it just like they put the date on it. All right.

Now again if you think this through, if I am doing an Alzheimer's genetic study my answer to those questions is I am not going to provide any of the results. They are too interim and there is nothing I can do about them. All right.

So to me if I am writing this "rec" the last question I then ask the commission for a sense of the commission is are you going to tack on at the end of it provided, however, if the research study was conducted under a waiver of consent there will be no go back under any circumstances. Do you want to tack that on or not?

Well, you have got the criteria that are laid out here about when you would go back. All right. So you just need to -- if the sense of the commission is that even in the absence of consent to the study, under a waiver of consent if you have a finding that meets these thresholds, it looks rock solid, it is certain, all right, it is an immediate threat and there is something that can

be done about it, even then you can go back and it is easy to -- you do not tack on that provided however.

DR. MIIKE: My answer would be that I do not have a problem with --

(Simultaneous discussion.)

MR. HOLTZMAN: Again, I am looking for the sense of the commission.

DR. MIIKE: I do not have a problem with saying that, you know, we recommend that these are guidelines but it is not a hard and fast rule that says that --

MR. HOLTZMAN: Those are only guidelines, Larry.

DR. MIIKE: Fine.

MR. HOLTZMAN: Those are only guidelines.

DR. MIIKE: Fine, but that is what I am saying. I do not think we should back an IRB into a corner that they have no discretion to make on an individual case.

MR. HOLTZMAN: That is what this says. They have to -- okay.

DR. MIIKE: I mean, guidelines are not

mandates.

MR. HOLTZMAN: All right. I will write --

DR. SHAPIRO: I understand -- I would not agree with that last phrase, I believe, as I understood what you said. You are asking what people believe. That is what I believe from what I understood.

DR. BACKLAR: Did you say you would or would not?

DR. SHAPIRO: Would not.

MR. HOLTZMAN: Okay.

PROFESSOR CAPRON: Reilly does not fully spell out here but I think the suggestion in all our conversation is that at that point the investigator comes back to the IRB and presents the situation and we are talking about an IRB which started off believing that there was minimal risk, that is to say nothing that is found here -- which our plan is not to disclose because this is a nonconsent situation -- it poses any risk to anybody.

So the anticipation is that what we are looking at does not have the potential to set us up in the situation where we have data vital to someone's life that

they do not have and we cannot give it to them. That would be more than minimal risk and it would require consent it seems to me if you know going in.

So we are talking about those rare situations in which something comes out of the research that was not anticipated. Isn't that right?

(Simultaneous discussion.)

PROFESSOR CAPRON: Otherwise you do not have a waiver of consent.

DR. CASSELL: HIV was a situation like that where serum pools existed that had -- nobody knew what was in those serum pools and they went back and studied those serum pools. I mean, there are --

PROFESSOR CAPRON: Right, exactly.

DR. CASSELL: There are precedent to this.

PROFESSOR CAPRON: Exactly.

DR. SHAPIRO: Tom, could I suggest that Steve and staff and the others just draft this now for us to look at and we get on to something --

DR. MURRAY: Yes.

DR. SHAPIRO: -- another subject?

DR. MURRAY: It seems like we have -- Steve,

do you feel -- it looks like you are the default chair of this little working group here.

MR. HOLTZMAN: I am writing it.

DR. MURRAY: Okay. Good. Thank you.

Shall we -- number nine caused us problem yesterday. We do not think that we reached closure on recommendation number nine, which seems to combine two different things.

One is that researchers ought to give thorough justifications of research design, which in the view of some members, including myself, does not add anything to what we think is already the understanding of what researchers are supposed to do when they go before an IRB, and then a second thing, which is where studies pose risks to others IRB should exercise heightened scrutiny and there is a problem here in that the others mentioned in this parenthetically are groups and not family members. So that is where we were as I remember.

Harold?

DR. SHAPIRO: My recollection is we decided to drop nine and pick up any aspects of it that we thought were important in other areas. Either they were redundant

or it needed to be picked up elsewhere. That was my recollection.

DR. MURRAY: Is that a shared -- okay. I see no dissent from that then. Fine.

Number ten. Alta?

PROFESSOR CHARO: I do not have a problem with the content of ten but I think the tone may be slightly off because it struck me as discouraging researchers from using identifiable samples and elsewhere we have wanted to encourage them so I just wanted to suggest that we pay attention in the rewrite to that issue.

DR. MURRAY: Could I ask anyone for an elucidation of what ten is intending? I am having a little trouble figuring out what it is supposed to -- what it is trying to say.

DR. CASSELL: Well, it seems to me that it is just like nine. I mean, that is the part of the study design. That is -- somebody has a design and they provide a routine justification for their research design. This is just part of it. I do not see what this adds to what we thought before about nine.

DR. SHAPIRO: I think -- just reflecting back

on the conversations either from last time or two times ago as to the origin of this quite aside from whether one agrees with it. There was some discussion here about whether people would strip identifiers as merely one way of getting -- avoiding the review process and there was some concerns expressed by some commissioners that that was not always appropriate. This was -- that is where, I think, the origin of this is just to try to respond to your question. There was --

PROFESSOR CAPRON: Does that suggest --

DR. SHAPIRO: -- that is my recollection.

PROFESSOR CAPRON: Does that suggest that -- in response to that comment and Alta's that what we are really saying here is that they should provide a justification if they intend to strip identifiers rather than seeking consent?

DR. SHAPIRO: That is my impression.

(Simultaneous discussion.)

PROFESSOR CAPRON: I will just write that down.

DR. MURRAY: That is good. Thank you, Alex. Does that capture the sentiments?

DR. SHAPIRO: Yes.

(Simultaneous discussion.)

DR. MURRAY: Bingo. Good.

MR. HOLTZMAN: Can I ask a quick question?

DR. MURRAY: Steve?

MR. HOLTZMAN: I found myself writing in here that there should be a justification for the decision to use identifiers and whether they intend to seek consent, seek waiver of consent, or strip identifiers.

PROFESSOR CAPRON: Well, the stripping identifiers is probably attached to seeking a waiver, isn't it?

MR. HOLTZMAN: No. You can seek a waiver without using linked. Right?

PROFESSOR CHARO: Yes.

MR. HOLTZMAN: You could say I am going to use linked and then I can seek a waiver of consent. So you are talking -- so I think --

PROFESSOR CHARO: If I may, Steve, one of the difficulties but I do not think it is lethal and I do not want to spend too much time on it, one of the difficulties is that if somebody is going to strip the identifiers they

do not need to go to the IRB at all because they are no longer going to be doing human subjects research and they will not be having to provide any justification to anybody.

This may, however, rise in more complex situations of multicenter, multicollaborator scenarios in which there is a requirement for all the centers to have passed on something because I actually am in a situation where I need IRB review and my collaborator is going to strip identifiers so he does not really need to go to his own but he has to check in with them because my IRB requires his IRB to look at it. So I think this provision is going to come up rather rarely. If they are going to strip identifiers most of the time they will not go to the IRB at all. They will not be justifying. Occasionally it will be done as a favor to a colleague.

Most of the time what will be happening is that people will be coming into the IRB. They will be using identifiable material and they will be explaining whether they want to get consent or seek a waiver of consent, which is part of the usual routine there, and in that fashion this kind of collapses a bit. It collapses

into nonuse, this recommendation a little bit but it is not lethal. I mean it does not --

DR. MURRAY: You think it is still useful to keep it in.

PROFESSOR CHARO: It might still be useful to keep it in. I mean I am perfectly willing to just see how it all falls out the next time around. We might strike it then or keep it in.

DR. SHAPIRO: And it may appear elsewhere in the text as opposed to the recommendation.

PROFESSOR CHARO: It may be more of an explanation of how these decisions are made and where the decision points are and who is looking over your shoulder.

DR. MURRAY: We are going to move on to the consent recommendations in a moment but Larry wanted to say something.

DR. MIIKE: My recollection of the issues behind this one was that we did not want to get into a position where less than optimal research would be done by researchers because of the obstacle of getting consent with identifiable samples and so they would say, "Well, then I am going to strip it and then do bad research."

That is what we were trying to prevent.

So I do not think it adds to have a recommendation around this because we are trying to -- we are recognizing the problem that -- like David was saying, the future is identifiable sample research and we are trying to make that easier and still make a balance. So I do not know whether we should even have a recommendation. It does not capture what we had wanted to do.

DR. MURRAY: Carol has the last comment on this.

DR. GREIDER: Just following up on what you both said. It seems more like it is instructions to investigators about things to think about, that they should justify whether or not they are stripping identifiers and why they are doing it. It is not really instructions to an IRB because of Alta's point.

DR. MURRAY: I am going to reserve for myself the last word on this particular subject. I think Alex's redrafted language is useful in any case even if we choose to have it as part of explicatory text rather than a formal recommendation but it will be very helpful. So let's move on.

I know Jim Childress needs to leave soon. Let us move to consent. The recommendations concerning consent. Jim has some comments he wants to share with us.

DR. CHILDRESS: If I could make a couple of comments about consent and then add a couple of other things with the indulgence of the chairs.

First of all, it seemed to me to be arbitrary and unhelpful to distinguish process and form and document here. There are overlapping materials and it would just be better to go ahead and talk about consent and include the references to forms and process underneath. So that would be the first thing.

Second, it seemed to me, and I do not have a lot of concrete suggestions to offer at this point, I will think further about it, that several of these could actually be grouped together in significant ways and produce the list of items.

But with the indulgence of the chairs I would like to make two other points. The point I raised two meetings ago, and I missed the Princeton meeting, still seems to me to be a problem in this chapter and maybe in the report as a whole, and that is our effort to group the

four types of research samples into two categories of unidentified -- of unidentifiable and identifiable becasue this really leads to oddities in the text when we are trying to explain that. Sometimes we talk about something is unidentifiable when it is impossible to establish or reestablish the link.

But often we talk about it in terms of it being difficult and it produces a difficulty. And it seems to me that -- just to use one of the recommendations as an example of the kind of problem we get into if we do this kind of grouping, on page 38, recommendation six, it talks about unidentifiable samples that were obtained cannot by definition be identified.

Now if we take that seriously then we cannot go back and talk about degrees of difficulty or ease in identifying. I would urge us -- it may well be we end up treating for practical purposes, for instance, the unidentified and unlinked in terms of what we are recommending in the same way but that does not mean we ought to call them the same thing and I think calling them the same thing leads to confusions in the text.

And led me, for instance, at one point where

we talk about identifiable that is in quotation marks. Now how am I to understand that? Is that meaning it is just one of those versions or both?

So I really feel very strongly that this will work a lot better as a report. Even again if we group our recommendations by saying that we are going to make them the same thing for unidentified and unlinked and then coded and then identified. I think calling them by these labels will be a mistake.

The last point quickly is that I hope -- and I have not seen the revisions that are underway of the earlier chapters but we have certainly said a lot over the last day-and-a-half about the way in which these recommendations will really be supported by what appears before.

I have a little bit of concern there because early on there were critiques of the ethics chapter and recently I have seen a long critique of the document. You sent me a copy of it. And there are some sharp criticisms being leveled against the kind of just listing of interests and, you know, balancing that we take there. And it is not clear that we provide the foundation there

for coming to these solid recommendations here.

I think there is going to be a lot of work in connecting -- especially the argument in the ethics part -- with the kinds of conclusions we are coming up with here. So a kind of cautionary note. I think we have a lot to do there if we are really going to make that stick unless we are going to put a fair amount of explanation and justification in relation to the recommendations we are offering here.

DR. MURRAY: Carol?

DR. GREIDER: I would just like to second Jim's comment about keeping the four categories as four categories. I appreciate you saying it first this time, Jim, since I said it at the last couple of meetings. I also was not at Princeton so I do not know the discussion that went on about this.

But as I recall we have had this discussion before and the text has changed around this but still on page 11, although we have all of the text leading up to the four kinds of categories, it really goes back to lumping the two and giving them a name, and one of the ways that I thought that we felt comfortable moving

forward was to treat them similarly but continue to call them differently. So that is just a second to what Jim just said.

DR. MURRAY: Kathi?

DR. HANNA: I would appreciate if we can adopt this at this meeting. At the Princeton meeting your request was overturned.

DR. GREIDER: I did not know.

DR. CHILDRESS: I did not know that.

DR. HANNA: And so I -- I mean, every time we redraft it, it would help if we could have the sense that it was going to stay that way. It makes it much easier to rewrite the chapters.

DR. SHAPIRO: There are two problems here. One is that some of the text remains unchanged because of word processing problems. That is still not completely eliminated here in my view but it is a lot better than it was. Most of them are caught. That is where we changed -- this was not to do grouping four versus grouping two but had to do with whether impossible or very difficult if you recall that discussion. And we decided on the very difficult and not the impossible.

But as far as I can tell, whether we group them or do not is a matter -- is not a great, in my view, matter. So that if people feel better having it separated, fine. It is just a matter of how the sentences sound more than anything else. And so I am perfectly happy to go and use all four categories or mention both in every sentence that we have to mention it. That is not a big issue to me.

DR. GREIDER: Can someone just tell me why, just briefly in a couple of sentences, it was changed at Princeton? Why people felt that we should go back to -- because it has never been written in the draft. I have never seen anything on paper that has had four categories but we discussed it in D.C. two times ago and I thought that we had agreed to keep four. And then I have not seen anything on paper.

DR. HANNA: Alex was the one, I think, who had the concerns about using two terms. You had concerns about using two terms. You thought if it is unidentifiable just call it that and if I recall you were the one that wanted to remove the language that said unlinked and unidentifiable over and over and over again.

PROFESSOR CAPRON: Yes. I thought once we had explained that we were using the term one way we should -- it just reads much better than constantly having these slashes.

I do not think we -- I disagree that -- if we are clear as to what the meaning is I disagree that we add anything by constantly reiterating it and what actually I think provoked the discussion was there were times when we used one of the two terms and not the other or, you know, it just was --

DR. CHILDRESS: Alex, I guess the thing that would help me is what is the common sense understanding of unidentifiable.

PROFESSOR CAPRON: Those which do not have names on them because they come from anonymous basis or those which --

DR. CHILDRESS: No, no, I am trying to understand what it means to say something is unidentifiable.

(Simultaneous discussion.)

DR. CHILDRESS: It cannot be identified at all or that it can be identified only with difficulty.

DR. CASSELL: It is impossible.

PROFESSOR CAPRON: It is like are there any white ravens? No. I mean, I think it is not a --

(Simultaneous discussion.)

PROFESSOR CAPRON: The notion that it cannot be done we have heard so often from the geneticists. The whole point of the genetics is that if they have a sample and they get another sample from you they can say, "Oh, this was your sample," because they can do a genetic analysis. None of the records that were existing are the route for that.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I believe that Alex is correct that we have clearly defined these in the text. However, I believe --

DR. CHILDRESS: They were not defined in this text.

(Simultaneous discussion.)

MR. HOLTZMAN: No, in terms of putting the buckets together. Okay. That is these two go into one. However, I would vote even if it is not the most eloquent writing to keep them four separate ones in all instances

being very clear and my reason is that this report will become -- will join a constellation of reports, all right, which use terminology very variously. We cannot assume people will read every line of this report. They will turn to the recommendations in chapter five, for example.

We heard yesterday that in the medical information privacy area it is very likely that they will have a different set of nomenclature. Okay. And it is going to be very important to understand how one nomenclature hooks up with it. And if you go through the public comment we got this was the subject of much, much public comment about an unclarity as to why we were putting what where.

PROFESSOR CAPRON: I think that the public comment we got and the comment yesterday was that they are simply taking the view that coded samples fall into what most people think of as an unidentified category and we take a different view for reasons that we began to explore and we have talked about all along that biological data are different than a cover sheet or a sheet that is submitted to an insurance or Medicare or something that has a discrete set of information on it.

DR. MURRAY: Despite my great affection for supple and succinct prose I think misunderstanding creeps in so frequently, and I often found myself reading the text whether to write sample or specimen, wondering what was the right term there, which we do not need to do that, but I think probably this is one case where over specificity is reluctantly warranted and I would just -- maybe should we put it to a vote or is there a consensus about this?

DR. CHILDRESS: Yes.

DR. MURRAY: Is there a consensus? Put it to a vote.

(Simultaneous discussion.)

DR. MURRAY:

So the question here is to basically take on Jim and I think Steve's recommendation to -- even though it may not be pretty -- to be very clear at each point which of these categories we are talking about rather than to lump the sets of two -- the two forms, the coded and unidentified as specimens as -- we have lumped them as identifiables -- as unidentified -- wait a minute. Unidentified is the same. Whether to abandon that effort

and in every case to spell out what -- for each of the four categories what we mean. That I think is -- am I correct that that is what the proposal is, Jim?

DR. CHILDRESS: Yes.

DR. BRITO: Can I --

DR. MURRAY: Yes, Arturo.

DR. BRITO: -- before you go on. For clarification then does that mean that once you do that, making four categories and you are going to specify each one, that on pages 11 and 12 you are going to get -- and 13 -- the unidentified samples of identified samples, that is going to be eliminated? That description. Is there no place for this anymore?

DR. _____: Just substitute two words for one word.

DR. GREIDER: It is on page 10, 10 and 11, those are the four samples.

DR. BRITO: Right.

DR. GREIDER: And then on the second half of 11 and 12 is the linking. So some of that text will have to be rewritten.

DR. MURRAY: That is right. I think that is

right, Arturo. We will -- we can allude to this and say some people have done this but for the purposes of clarity in this report we shall specify --

(Simultaneous discussion.)

PROFESSOR CAPRON: I think Arturo is right that there is a substantive discussion on pages 11 through 14 that is going to have to be reworked to provide understanding even if from now on in -- as I understand the proposal it is not to create -- well, actually two things were said. Jim suggested that we almost have -- and Carol said -- duplicative recommendations.

If the suggestion now is to replace the word "unidentifiable," this is basically a word processing thing, you go through and replace unidentifiable with unidentified/linked.

(Simultaneous discussion.)

PROFESSOR CAPRON: And linked or unlinked.

DR. MURRAY: Right.

PROFESSOR CAPRON: It is not an "or." It is a slash. It is these two categories.

DR. MURRAY: It depends. It can be and it can be or depending on the case --

(Simultaneous discussion.)

PROFESSOR CAPRON: It is going to be one or the other.

DR. CHILDRESS: The text is talking sometimes only about one of those and that is --

PROFESSOR CAPRON: That is my -- I agree. So it is whatever the wording is or -- that is all we are doing. We will have the same recommendations. It is just each time we will repeat two words or three words instead of one word.

DR. GREIDER: So most of the text on 11 and 12 and 13 can stay as to our justification for considering these two together but --

DR. MIIKE: Carol, why don't you just go over the chapter and change it to your liking and then --

DR. GREIDER: I have four times.

(Simultaneous discussion.)

DR. MURRAY: We are going to put this to a vote. The vote to retain the specificity as Alex just outlined. All in favor of doing that please indicate by raising your hand.

(Simultaneous discussion.)

DR. MURRAY: Well, Alex just outlined how we are going to do it.

DR. SHAPIRO: Four versus two.

DR. MURRAY: Four versus two. That is what --

DR. GREIDER: Okay.

PROFESSOR CAPRON: Two subsets always together but words used. That is what we are saying.

DR. CASSELL: Four versus two.

DR. MURRAY: Four versus two.

PROFESSOR CHARO: Do what Jim asked.

DR. MURRAY: What Jim asked. All in favor of doing what Jim asked.

DR. CASSELL: Wait a minute. This is four?

DR. MURRAY: Yes, four.

(Simultaneous discussion.)

DR. MURRAY: All for four?

(A show of hands was seen.)

DR. MURRAY: All for two? Passes. All right. With no dissents.

DR. MIIKE: Just one last comment, just to make sure that in the chapter we point out that we are reaching different conclusions about the coded samples

because that is the main distinction that we are making.

DR. MURRAY: Yes. Right. Okay.

(Simultaneous discussion.)

DR. MURRAY: Jim?

PROFESSOR CAPRON: Now I have a question for Jim. When we say an unlinked sample is one -- are saying that extreme difficulty? Page 10–-the whole discussion of what unlinked means.

DR. CHILDRESS: I have no problem with that.

PROFESSOR CAPRON: And what does that mean to you?

DR. CHILDRESS: I have no problem with the statement.

PROFESSOR CAPRON: What does it mean to you?

DR. CHILDRESS: That it is extreme difficulty. It is not language I put here. I do not get any particular interpretation but I am comfortable with the way it --

(Simultaneous discussion.)

DR. CHILDRESS: It does not mean impossibility, though.

PROFESSOR CAPRON: Virtually impossible,

highly unlikely. But I would like -- extreme difficulty is a statement about effort. I would like a statement that tells me how likely it is.

DR. CASSELL: Highly unlikely

(Simultaneous discussion.)

DR. CHILDRESS: I did not choose the language of extreme difficulty. Whoever put it in can support it on 10 and 12 and the other places it appears. I am not giving it a particular content.

DR. MURRAY: Bette?

MS. KRAMER: Apropos the same point. When we same extremely difficult on 10, on 11, line 24, we say, "Nor anyone else can ascertain." In other words, it is no longer extremely difficult. It is absolutely impossible.

DR. MURRAY: We will have to clean the prose up so that it does not contradict itself. I do not know who put the language "extremely difficult" in. It is okay by me if it stays in.

DR. MURRAY: Do we want it to read anything other than extremely difficult? Is that a phrase?

MS. KRAMER: If it reads --

DR. MURRAY: That is what it reads right now, Bette. If you want it -- we will clean up inconsistencies --

MS. KRAMER: Right. Okay.

DR. MURRAY: -- but the question I am asking you is solely what phrase do you wish to use to describe it.

MS. KRAMER: If it reads "extremely difficult" then there has to be language somewhere that supports why we have said it. It is because if the right number of people and the right places get together they could break the code or something of that sort. And maybe it is there. I do not know. Otherwise --

PROFESSOR CAPRON: There is no code. Unlinked. There is no code. See I --

DR. MURRAY: This is --

PROFESSOR CAPRON: -- we are still -- what we have just decided is --

(Simultaneous discussion.)

PROFESSOR CAPRON: -- use the two words but put them together. We have to explain why they are together. They are together because of some statement

about how unlikely it is that you would be able to identify. I mean there is some reason for grouping them. Using both the words has not removed that problem. And if that was the central problem that moved Jim to say we ought to use the two words, my point is we have not answered that. We have not gotten beyond that. And as Arturo said, we need to -- we still have the language on page 11.

MS. KRAMER: I have a proposition.

DR. MURRAY: Bette?

MS. KRAMER: I have a proposition. At some place in the text we need to say that what we have referred to -- and it is probably somewhere in there -- that if the sample were small enough -- it is in there. If the sample were small enough the conditions under which unlinked samples, given proper tests, et cetera, could be identified. However, we have chosen to call it unidentified and that is it.

DR. MURRAY: Well, we are not calling it unidentified. We are calling it unlinked.

MS. KRAMER: We are calling it unlinked but we are treating it as --

DR. MURRAY: We are treating it --

(Simultaneous discussion.)

MS. KRAMER: -- unidentified. Right.

DR. GREIDER: We are treating it in the same way as we are treating the unidentified samples.

(Simultaneous discussion.)

MS. KRAMER: Can we then footnote if it is a problem, footnote the phrase "extremely difficult" with a reference to where it is explained so that if somebody just picks up the recommendation -- if they pick it up without reading the whole thing and they read this and they say it is extremely difficult --

DR. MURRAY: There are two things that are being conflated here. One is simply what descriptively we mean by the standard of extremely difficult and two is what our justification is for treating for most purposes as if it were -- in fact, treating it equivalently as if it were completely unidentified.

We shall do that. We shall describe it and we shall also offer a defense of why we will under most circumstances treat it in the similar fashion that we treat completely unidentifiable. I think that is a fair

request and we should do it.

Larry?

DR. MIIKE: I am going to contribute to my own criticism but I think we are spending too much time on this unlinked area. It is the other side that people are going to be concerned with. That the coded areas we are now saying are unidentified. And on the unlinked side I do not think we are going to have that much problem and it will be obviously in the kinds of areas where you have unlinked samples which very easily can be identified. If you have 15 people living in an Alaska Native village and they are unlinked but you have their age and their sex everybody knows who they are. So we are always going to have those kinds of problems.

So I think that all our concern about this definition about linked is -- we do not need to get into it.

DR. MURRAY: Well, are we comfortable with making the distinction between the description of the concept and the justification for treating unlinked as so defined similarly with genuinely unidentifiable? If we are comfortable with that we shall do that and then we

shall move on to the recommendations. Okay.

Jim -- one of Jim's suggestions, and I am sorry he had to leave because Jim is a real resource for these questions, was to recombine, rearrange and recombine some of the recommendations on consent. Alta also raised an issue about assigning teams to rewrite recommendations. To have people working in isolation without some over arching concept of how things might be recombined might be counter productive.

So let us as we look through these recommendations -- in fact, why don't I invite you to read for a minute 11 through 18, all of which concern consent.

Larry?

DR. MIIKE: A comment about -- I guess a lot of these -- actually they can be combined into subsets of a larger one. Are we going to keep 13, though? Thirteen gets into this whole issue about interim findings. It seems like that is a particular part of the consent process that we do not need to include in this area because the others are more like, hey, let's keep the clinical consent separate from the research consent. Obviously we -- then part of that consent is to tell a

person, you know, you are not going to get effective clinical care if you refuse the consent. Those kinds of things. But this one sort of sticks out like a sore thumb.

PROFESSOR CAPRON: I thought when we were talking a little while ago the thought was that we would have a set of recommendations about the recontact problem. I agree with you this would more belong over there.

DR. MURRAY: Steve?

MR. HOLTZMAN: However, there is a -- this would be a call for a decision by the commission. There is a reading of 13 which says you must offer the people the opportunity and option to get interim results. Does the commission support that or doesn't it? This commissioner does not.

DR. SHAPIRO: Not as a must I would not. This is my own view.

DR. MURRAY: Okay. Is there anyone who dissents from that view?

(Simultaneous discussion.)

MR. HOLTZMAN: Again, I mean it should be offered. Okay. So that was not the sentence. Right.

Then it can be folded in. Okay.

DR. MURRAY: Right. We have made a decision. So we are going to pluck the current 13 out and put it in with the recontact set.

PROFESSOR CAPRON: And revise the first sentence.

DR. MURRAY: And revise the first sentence as so stipulated. And I think it should then go to the group that is rewriting the recontact. The recommendations dealing with recontact. So --

DR. _____: That would be you, Steve.

DR. MURRAY: That is Steve's team. Okay.

DR. CASSELL: I want to make a comment about how good this set of consent ones are in general and you can understand them. They address the issues. They are excellent except we do have a confusion with terminology in 17(B) but otherwise they are clear.

DR. MURRAY: Eric, do you have -- would you want to combine any of these?

DR. CASSELL: No, I like it this way.

DR. MURRAY: As separate.

DR. CASSELL: I like them separate.

(Simultaneous discussion.)

DR. CASSELL: Somebody said you have got to put them together in one element, I do not know about that, but the advantage of separate is that they are clear. But if you want to say this is all part of the statement about what kind of -- what should be in a consent form, fine. Okay.

DR. MURRAY: Carol?

DR. GREIDER: I just have a question and maybe somebody can answer this about 18. Eighteen seems to be somewhat different than what we were talking about before. So this has to do with informing people about the extent to which medical records are kept confidential.

Is it necessarily true that findings would even end up in their medical record in the first place? To my knowledge, research findings do not go into the medical records so why are you telling people about the degree to which medical records are confidential. I am not sure how this fits.

DR. HANNA: Alta is not here. But she -- this was one of her suggestions and recommendations. I think there are two things here. One is that it is apart --

DR. CASSELL: Could you turn that microphone on?

DR. MURRAY: It is on.

DR. HANNA: First of all, it is not research results going into the medical records. It is investigators having access to and collecting data from medical records. So if that is not clear it needs to be made clear.

The other thing is that my impression is that this is routine. It is supposed to be part of the consent process anyway. So we might want to wait until Alta gets back to ask her what she had in mind here. But it was not putting research results into medical records.

DR. MURRAY: I have Steve and Diane next.

MR. HOLTZMAN: I had a question about 17 and you may have been discussing it because I am trying to write simultaneously and missed it.

DR. HANNA: No, we have not.

MR. HOLTZMAN: Okay. First, in the clinical setting we are really talking about the potential future uses of the materials. Correct? And we want those forms to say “Do not use it.”

Second, is I think we want to use the terminology that we use in this so when we say "sever all links" we should probably reference what we call that kind of sample.

And then in the third again I think we are talking about coded samples, right. Again I think it is important to reference.

I think it was also the sense of the commission that the use of identified direct -- what do you call it? Is it directly identified? Is that what we used as the term? That the consent to future research with directly identified is not possible. That is not informed consent. Right. I think that was something we have talked about often and, therefore, that should not be an option that is made available. So in the sense in which we are talking about (C) it only could be coded.

DR. MURRAY: Does that capture other commissioners' understanding?

PROFESSOR CAPRON: No. Because the coded is equally problematic there. Your other statement -- I think it was Harold who said it quite strongly at the last meeting that the notion that one would give blanket

consent for what we were then calling identifiable uses of his/her material for unspecified research for an indefinite amount of time-- something seemed just wrong with that.

MR. HOLTZMAN: So I --

PROFESSOR CAPRON: Coding does not get rid of that.

MR. HOLTZMAN: Okay. So I will argue that it does and that if one looks at what is the definition of informed consent, integral to it is the ability to make an objective evaluation of the risks and benefits. All right. And I think the argument that says with directly linked one cannot make that assessment because if one does not know what the research is, he/she does not know how it could impact his/her.

However, if one has a sufficient confidence in the coding and confidentiality scheme, I believe it is logically possible in line with the definition of informed consent to make that assessment.

And so if you are saying that that is not possible, I need to hear the argument and I can tell you -- all right.

DR. SHAPIRO: I would not argue that it is not logically possible because I think it is logically possible.

MR. HOLTZMAN: But I think it is important. That is the point, though. What is -- is informed consent possible? That is the question in play here. It ought to be the question in play.

DR. SHAPIRO: My opinion is that it is not. I do not know whether to use the word "possible." When I try to think of many subjects, trying to really have a meaningful assessment of all the probabilities here given the technologies that are around I despair and do not have much confidence in that, although I think for some people it might be quite possible for them to reach that assessment.

I think it is more likely that people reach misassessment in their situation and, therefore, need some protection. This is my view. I understand it is certainly logically possible.

(Simultaneous discussion.)

MR. HOLTZMAN: No, I mean I am really making a -- I am making a very -- I mean, it is not a question of

logically possible or not. I think what we need to be doing is looking at the concept of informed consent --

DR. SHAPIRO: I understand.

MR. HOLTZMAN: -- very carefully and asking the question what kinds of consents actually can be informed consent. All right. And I think if we are saying that the consent to future unspecified research with coded and confidentially maintained samples cannot be done -- are you saying -- are we saying it cannot be done or, well, it can be done but we do not think it is a good idea. I mean, we are saying one or the other.

DR. SHAPIRO: I think it is unlikely to be done rather than cannot be done.

MR. HOLTZMAN: Okay. All right. Well, I can tell you that right now standard practice, all right, reflecting a certain kind of judgment about the meaning of informed consent is getting consent to future undisclosed research with coded samples.

DR. SHAPIRO: I understand.

MR. HOLTZMAN: So this is a recommendation that standard practice in many places will be radically changed and I do not understand the basis for it.

DR. MURRAY: Let me just say I have -- I went out of the list. I have Diane, Larry and Bette on the list. If you are speaking to this point why don't you speak now. If not, can I just ask you to hold and we will try to settle this point.

Diane, first crack.

DR. SCOTT-JONES: Okay. I think I am speaking to this point but I actually had it in mind before Steve made his point and it goes back to that recommendation five that we discussed yesterday that refers to the issue of general consent for research given in relationship to a clinical or surgical procedure and there we said that it must not be presumed to cover all research over an indefinite period of time and that the documents should be reviewed to see whether subjects anticipated and agreed to the type of research.

So in that part of this document we have already said that that kind of informed consent to some future undisclosed research cannot be given so to be consistent we would have to change that language there.

And I would also recommend that we move that recommendation to this section. We talked about that

yesterday. And I think number 11 and number 15 also have some bearing on this issue of giving consent and perhaps they should be at least following one another to give this full picture of how you give consent in relation to some clinical situation and what informed consent means in that regard when you do not know what all of this possible future studies could be.

DR. MURRAY: Okay. I have Larry, Bette, Alta and Carol on the list but I want to ask Steve a question.

Steve, if Diane has -- if Diane's understanding is your understanding why did we --

MR. HOLTZMAN: Well, first of all, well, I satisfied myself, all right, that shall not be presumed to cover all forms of research on an in depth and indefinite period, I took the presumption. Okay. And I said it was not worth getting into a long discussion about it. Okay.

All right. But again that was my reasoning to let it go and again I do not know about anyone else but I spent a lot of mental energy thinking through what does it mean and when is it possible to give informed consent. I think we had this discussion and maybe we just never clearly articulated it to ourselves.

DR. MURRAY: Larry?

DR. MIIKE: Again I think this discussion revolves around trying to put too much stuff in any one specific recommendation. To me the choices are clear. One is that informed consent should make it clear in lay language to the person who is going to sign it that he/she does not want the researcher to use his/her tissue or the researcher can use the tissue but take the subject's name off of it, or the researcher can use the tissue or the researcher can go ahead and use the tissue with the subject's name on it.

And then the other parts of our report put conditions upon those uses. So we cannot really address it all but try to get all of those in. If you tell me, you can use it but we are going to code it, I would not know how to answer any of those kinds of questions. So we have got to have it in a fairly straightforward manner.

DR. MURRAY: Let me ask how that hashes out for 17(C). Would you feel it is okay to leave that language in? I can give sort of some consent for research?

DR. MIIKE: Yes. Something along -- I mean, I

would prefer just short sentences.

DR. MURRAY: Okay.

DR. MIIKE: But, yes, I mean --

DR. MURRAY: All right. Thank you.

Bette, Alta and Carol.

MS. KRAMER: No, basically I will second that because I have been thinking of conditions under which I would be willing to give consent for future uses.

DR. MURRAY: Alta?

PROFESSOR CAPRON: Could you explain that?

MS. KRAMER: Sure. I mean, suppose I was diagnosed with a terminal illness or supposing I was diagnosed with some condition that was just so endemic in my family that I say, you know, look, for whatever purpose the rest of my life can serve or after my life, after I am gone even, by all means go right ahead.

PROFESSOR CAPRON: Including all other conditions?

MS. KRAMER: Sure. What difference does it make? I am not going to be here. If it is going to help out --

DR. MURRAY: If you are not here you are not a

human subject anymore.

MS. KRAMER: I realize that.

DR. MURRAY: But we hope you are here.

MS. KRAMER: I mean, this is -- but seriously in anticipation.

DR. MURRAY: Yes.

MS. KRAMER: I could feel that way.

DR. MURRAY: Alta?

PROFESSOR CHARO: First, my apologies. I was outside talking to a member of the staff about the comprehensive report and I missed the beginning. So I am definitely a little confused as to why you are so agitated since it seems to me -- putting aside the particular wording -- the purpose here is to say that people can, in fact, make it easier for everybody in the future to use their stuff, which I thought is something you would approve of.

I do not find it difficult to implement this because we worked through it in Wisconsin and provided those documents to the staff which give one example of what seemed to be an adequate degree of notice to people of what we called the wide range of possible uses. We did

not try to catalogue them.

It did not take more than a couple of sentences to give them a hint to the fact that some of it might be politically sensitive to them or culturally sensitive, et cetera, and then we actually gave them more options than these. Probably more options than some repositories wish to make it possible for them to give away their tissue and never have to be asked again about what could or could not be done with it but to have really given sufficient thought to it at the very initial moment.

And I thought that this would be something you would approve of.

DR. SCOTT-JONES: Is Alta speaking to -- who are you talking to me?

(Simultaneous discussion.)

PROFESSOR CHARO: No, I am actually not, Diane. I am looking at --

(Simultaneous discussion.)

PROFESSOR CHARO: It was the crossed eyes problem. My left eye does not look at anything. Only my right eye does. So I am looking at Steve.

MR. HOLTZMAN: Okay. If I understand Harold's

position 17(C) should be struck.

PROFESSOR CHARO: Why?

MR. HOLTZMAN: I believe Harold has said the idea of giving unfettered wide open consent to any and all future research purposes using samples which are linked to my identity is not something that should be an option.

DR. SHAPIRO: That is my view.

MR. HOLTZMAN: Okay.

PROFESSOR CHARO: Even with appropriate prior notice as to the range of uses and the sensitivities --

MR. HOLTZMAN: Right.

PROFESSOR CAPRON: One time notice.

MR. HOLTZMAN: Okay. One time without -- okay.

PROFESSOR CAPRON: Without recontact and without reconsenting. Is that what you mean?

DR. SHAPIRO: Yes.

MR. HOLTZMAN: All I was saying is I thought it was useful for conceptual analysis to break 17(C) into two plates -- in your mind into two things, right. And it comes down to can you give blanket consent to any and all future research purposes with your sample -- informed

consent to that -- with your samples where there is directly identified and coded -- Bette has articulated a position which says even in the case of directly linked I can make a rational assessment that it is cool, go ahead.

That is where the position I was in my head say six months ago and I sat and listened to people very eloquently, yourself and Alex, talk about what does it mean to give informed consent and the take home of that argument that I understood was that, in fact, whatever that consent is, whatever that exercise of autonomy seems to be, if I cannot make an assessment of the potential risks and harms it cannot be truly informed.

Therefore -- all right. Bette's kind of position should not be open.

Then I asked the question but what about in the case of coded. Could it be an informed consent to an unfettered research use? To me those are the issues that are in play. 17(C), while you were out of the room, I said is unclear what we mean by link directly coded. And then Harold said, reflecting the discussion and observation he made in Princeton, the impact of which would be that 17(C) ought not be available as an option.

Is that clear?

DR. SHAPIRO: I may be the only one who feels that way but that is --

(Simultaneous discussion.)

DR. SHAPIRO: -- the commission will have to decide for itself.

DR. MURRAY: Bernie, Eric -- I am sorry. Carol, Eric and Bernie are on the list.

DR. GREIDER: I do not have a problem with 17(C) as it currently reads and I just wanted to respond to Diane's comment that if we take five and believe -- I think it was five.

DR. SCOTT-JONES: Right, five.

(Simultaneous discussion.)

DR. GREIDER: And justify those two positions. My reading of this is that five is for stored samples that were given in the past under consent rules that we do not know what they were and we presume that they were not necessarily very good. Whereas, in 17 we are talking about designing a new study and going into the future and how would we like this to be done. That is how I justify those two things coming to different conclusions.

DR. MURRAY: I just want to clarify something. You said 17 was designed to deal with where subjects are being recruited for research studies. That is not how I read it. I read it that this is the sort of --

DR. GREIDER: Future. I did not say research.

DR. MURRAY: -- future research studies.

DR. GREIDER: Future studies or clinical.

(Simultaneous discussion.)

DR. MURRAY: Getting the samples. Okay. Yes. Eric and Bernie are on the list and then Alex. Eric?

DR. CASSELL: Just to something simple for the moment. On (C) if you rewrite it and just simply take out the words "to give consent for the use of their samples for research purposes that maintain the person's identity." Nothing is added by links between the research and -- it is all about samples.

And that also has to do with what Larry said about the simple things, maintain the person -- and the other one is on (B) to give consent for the use of their samples but only in a manner that removes the person's identity or makes them unidentifiable.

DR. MURRAY: Next is Bernie and then Alex, and then Alta.

DR. LO: Like many of us I sort of have this feeling of deja vu all over again and I'm trying to remember when we talked about this and when we decided this. I guess a point I have been trying to make for a number of meetings is that these recommendations -- this recommendation 17(C), which I support if we can rewrite it, really only makes sense in the context of the kinds of things Alta was talking about where people are really trying to develop ways of communicating to patients what the range of possible studies as far as we know today might be. What our current understanding of risks and benefits are. What protections are generally in place and what studies might be problematic so it is an informed decision.

I mean, one of the problems I have with the way this is split out in the consent form documents is that giving people a choice only makes sense if you have made a real good effort to try and have them understand what is at stake here.

I do not agree with the idea that it is

impossible to -- or so difficult to give people an understanding of what might happen in the future that should foreclose that option. I think that gives up -- I mean, we have heard a lot of testimony as to what the potential downstream benefits are of allowing this kind of research on existing human samples. It seems to me if we do not allow for linked samples in the future to be used with consent given today what we are doing is foregoing a lot of research.

I think what does not come through here is our sense of urgency that better ways of trying to inform people so that this decision for future research can be as meaningful as possible under the constraints without being able to predict the future needs to be done.

We have heard Alta mention it today, and meetings, you know, years ago that we had, people come and say this is what we are working on. We are working on tiered consent. We are working on this. You know, we need to really say, yes, it is hard to do. You cannot absolutely predict the future. There is exciting work going on and we want to get behind it for the purpose of allowing this material to be used in ways that are

beneficial.

You know, I go back way to these focus groups we had early on and sort of saying, you know, focus groups do not count but, you know, one of the things that people said is we want our materials to be used in a way particularly that leads to better understanding of the diseases that afflict me or my family but for other things as well and I think that sense of altruism and a sense people are willing to trust that investigators are going to be careful as possible, we need to sort of follow it up and I think the way to do that is to really encourage people to really make better the way of communicating to people what this is all about.

Having said all that I am -- I think we -- I really do think we need to allow for people to consent to research in the future that uses their samples as linked samples. If their name is actually on it, you know, or identifiable very readily I have some concerns. But I think to allow it to be linked both reduces the potential risk and I think is not out of line of the kinds of studies being done today that would gain the scientific benefit.

DR. MURRAY: I have Alex and Alta on the list. Trish has indicated a desire to be added. Let me ask each of you to speak briefly and then I want to put a couple of questions to the commission and then propose a way to get this one rewritten.

Alex?

PROFESSOR CAPRON: I think Bernie is correct in saying that there is great value in this potential line of research. I think he is also correct in saying it is a question of a burden. I think we ought to talk about ways of addressing that burden and not putting it all on the shoulders of subjects, a substantial percentage of whom will not understand the risks because they really will not be able to convey to them. I am sorry, I do not think we are able to anticipate all the kinds of findings and convey them in a way that is salient to people who are focused right now on having a tissue sample taken for a diagnostic purpose or for research study involving their own disease and the disease in their family and that is their focus.

It seems to me that that burden would be more equitably shared in the research process if we talked

about a person in that case consenting for future research provided that they will be contacted and given the opportunity to opt out of that research after being informed of its focus. It is content.

What that will mean is that repositories that intend to make this use are going to have some obligations to maintain current ways of being in touch with the samples. That will cost money. I do not see why we do not understand in these situations if we are talking about the great benefits that will come from this area of research that those benefits have costs and they should not all be in terms of the ethical risks to the subject.

I would, therefore, favor revising (C) to say give consent for the use of their samples for research purposes in an identifiable fashion provided that they will have an opportunity to opt out of those studies as they arise. In other words, as the use arises. Language of that sort. And I think that is a more equitable sharing of the relative burdens. If the benefits are so great they are justified. Those burdens are justified.

DR. MURRAY: Alta, then Trish, and then we will try to reach closure on this.

PROFESSOR CHARO: First, my apologies for mussing around over here but I am going to catch an earlier flight today.

First, I must say I share a lack of enthusiasm for your position so far, Harold, because of both the benefits and because of my belief that it is possible to give what would be understood as informed consent based on highly imperfect information.

I did make reference before to the fact that we had somewhat more nuanced options in the Wisconsin proposal and they included things that provide a middle ground such as allowing one’s materials to be used with codes that link these subject to the materials into the future but on the condition that I be recontacted periodically for new permission, et cetera.

I mean, the concern strikes me as being one about changing circumstances about the potential harms of that information.

One of the things that makes me comfortable even with this less nuanced approach, which I do not necessarily think has to be altered, although I have no objection to it being altered, is that there are other

protections that we have built in, in other places, that should handle some of that problem of new kinds or magnitudes of harm. One is the IRB review itself which is supposed to making sure that the benefits and harms are appropriately balanced.

Another is the common understanding that when circumstances have profoundly changed in the way that materially affects the underlying consents that it is routine that you try to go back so that there be kind of another permission that would say are even these better informed consents sufficient. And the idea is to minimize the opportunity for that but it is never completely eliminated.

And the third is that people have been given the option to let their materials be used in an unidentified way which is a way to cut the difference.

And so I would like very much for us to find with the other protections we have built in and possibly would be added options -- and one last protection, by the way, is the opt our provision which we have suggested as an add on even when further consents are not necessary. That we try very hard not to close the door on these.

DR. MURRAY: Thank you. Trish?

DR. BACKLAR: I actually agree.

DR. MURRAY: All right.

DR. SHAPIRO: I certainly understand the issue well enough and I understand even that I could be wrong. But I am not persuaded by the argumen. And I think the suggestion offered by Alex, namely an opt out, is one way to some compromised situation, or maybe you made a similar type suggestion. But I do not -- far be it for me to insist on that. But I just come to a different assessment and there is no use talking long about it.

DR. MURRAY: I have a proposal for how to get this recommendation revised but I want to make sure we understand where at least the majority, if not perfect consensus of the commission is. Do we, in fact, intend -- I am going to ask the commissioners to indicate by hand that there should be some provision similar to that currently encompassed in 17(C), whether it include an opt out or some other -- but some provision to permit that sort of consent that would prevent future research. All in favor of that?

It could be a generous one, Alex, with an opt

out.

PROFESSOR CAPRON: Well if we have the opt out.

DR. MURRAY: Well, I am asking -- because we are going to have this rewritten. All in favor of that openness please indicate by raising your hand.

(A show of hands.)

DR. SHAPIRO: I apologize. I am not sure whether to raise my hand or not simply because I know how I feel. I am not sure exactly what the question is. If it is broad enough to include who will be drafting this requirement for an opt out provision or something else that is in --

(Simultaneous discussion.)

DR. SHAPIRO: -- if it does not include that, which I think is probably what most of the people here have talked about, I just speak for myself, it --

DR. MURRAY: Let's take a straw poll. Who would favor it without an opt out provision? Something like 17(C) without an opt out provision.

(A show of hands.)

DR. MURRAY: Who would favor it with an opt

out provision?

(A show of hands.)

DR. MURRAY: Steve and Diane are not voting.

MR. HOLTZMAN: I voted for the first.

DR. MURRAY: You voted for the first. Okay. But you would favor it. Would you still favor it even if it had an opt out provision?

MR. HOLTZMAN: Is the opt out required?

MS. KRAMER: How about an opt out if -- the person has a right -- the individual has a right to elect the opt out? The opt out is optional.

(Simultaneous discussion.)

PROFESSOR CHARO: It is just an additional option.

DR. MURRAY: Thank you for that clarification.

MS. KRAMER: Try the vote again.

(Simultaneous discussion.)

DR. MIIKE: Could I just make a comment?

DR. MURRAY: Yes.

DR. MIIKE: I vote for an unfettered [inaudible] but only because this is not our whole report. We have other safeguards in the report.

DR. MURRAY: Right. Fair enough.

Diane, a clarification?

DR. SCOTT-JONES: Just a very minor question. Is it deliberate that on page 40 we are not saying informed consent process? We are just saying consent? Is that the reason -- okay.

DR. MURRAY: I do not remember. Is that deliberate --

DR. SCOTT-JONES: I just wondered because --

DR. MURRAY: I should ask the drafters. Is that a deliberate omission of the word "informed?" I do not think so. No. The answer is no. It is not a deliberate omission.

PROFESSOR CAPRON: So it will go in. For example, starting with number 11.

(Simultaneous discussion.)

PROFESSOR CAPRON: But the language of the recommendation --

(Simultaneous discussion.)

DR. MURRAY: All right. We are going to ask this again. If subjects, when they are initially asked to consent are given the option of consenting with an opt

out, that is that they could be asked to opt out in the future for further studies -- I am sorry, I am getting a little articulate here -- but they are given the option of asking for an opt out of --

PROFESSOR CHARO: Right.

DR. MURRAY: Who would approve of it with those terms?

DR. CASSELL: Wait a minute. Opt out is -- I mean, the consent says --

THE REPORTER: Will you use a microphone?

DR. CASSELL: -- have a chance to opt out. Is that what you mean?

PROFESSOR CAPRON: No, the consent form would say check off that you agree to the identifiable use of samples coded perhaps but make that clear.

DR. CASSELL: Right.

PROFESSOR CAPRON: And then say provided that you receive or without receiving further notice and an opportunity to opt out. You get to check between those two.

DR. CASSELL: Yes, okay.

DR. MURRAY: Okay. That is the proposal.

Thank you, Alex.

Who would be in favor of that proposal?

(A show of hands.)

DR. MURRAY: Who would not? Who would be opposed to that proposal?

DR. MIIKE: Tom, again it is a question of -- you see it is the -- the way it is stated it is absolute. Because in other places we talk about the reasonable opportunity to contact and opt out, et cetera.

The way we are talking about it is that if you do not opt out you cannot get -- I mean, you know what I mean? If we do not contact them to opt -- are we talking about the researcher having to make every effort to contact the person to opt out and if you do not then what?

PROFESSOR CAPRON: Then their sample could not be --

DR. MIIKE: Well, see, exactly -- so --

PROFESSOR CAPRON: There are going to be plenty of samples around. There are going to be plenty of samples. Once it is clear to the research community they need to do something they will do it.

I mean, years ago all these procedures did not

exist and the research community said we can never run research with these procedures. They have learned to do it. They have put the clause in. We have shifted some of the ethical costs from the shoulders of the subjects to the shoulders of the research process.

DR. MURRAY: Eric?

DR. CASSELL: Well, I actually would change my vote. I really did not understand it. I do not believe you should do that. You want to be recontacted when new research is done. I agree with Harold. You cannot consent to something in the future risks of which you do not know.

DR. MURRAY: Well, I am unsure if we have anything resembling a consensus of this point.

PROFESSOR CAPRON: You have a clear majority that thinks -- that does not agree with the chair.

(Simultaneous discussion.)

PROFESSOR CAPRON: It is very simple to put a little asterisk to go there and say Chairman Shapiro and such and such commissioners believe that the opt out should be a required part of -- you know. There is a division.

(Simultaneous discussion.)

DR. CASSELL: I agree with Harold. I think you cannot do that.

PROFESSOR CAPRON: I think it does not qualify as informed consent.

DR. CASSELL: That is right.

PROFESSOR CAPRON: It is too expansive and you cannot know what you are subjecting yourself to.

DR. MURRAY: Well, Alta is not here but I sense -- if I understand Alta she would disagree with that and Jim would disagree with that.

PROFESSOR CAPRON: That is right.

DR. MURRAY: So we --

(Simultaneous discussion.)

PROFESSOR CAPRON: I think you have a majority. Do not fight it. You have a majority. We are not all going to agree on this one.

DR. MURRAY: Okay.

PROFESSOR CAPRON: It does not --

(Simultaneous discussion.)

DR. LO: You said a clear majority. I did not see a clear majority.

DR. MURRAY: Let me hear Bernie's comment and then we will take another --

DR. LO: Let me suggest that given the history of this commission we are not going to settle this today even if we think we are. Why don't we try to write something that reflects real divisions not just in this group but I think in the community at large. There are some of us who feel that you cannot give prospective consent in such an open manner, you know.

And I think the position of Harold, Eric and Alex are espousing ought to be articulated here. This is one of the situations where just to give the recommendation even with a vote does not capture the issue We all share those concerns. Some of us are more pessimistic or optimistic as to whether those concerns can be addressed in a large number of cases.

We are going to disagree on how much.

I think some of that has got to be here. Otherwise, we are just --

DR. MURRAY: Bernie, in the interest of time could I just make a proposal? Let us designate a drafting team and they should come back with two alternative

versions of the recommendation. And I want -- well, Alta is out of the room -- Alta, Bette and Harold on this. I want both perspectives represented and they should come back with two versions and we should vote for one or another. Is that fair enough?

PROFESSOR CAPRON: And let me just offer one alternative could be have a (C) and a (D). The (C) -- because we are talking about options that will be offered to -- and then the dissent says that the three or four of us do not believe that (C) should be an option, which amounts to the same thing.

(Simultaneous discussion.)

DR. SHAPIRO: So we just have an easy option. It is not a hard thing to draft.

PROFESSOR CAPRON: It is not.

DR. SHAPIRO: We can do that.

PROFESSOR CAPRON: But it --

(Simultaneous discussion.)

PROFESSOR CAPRON: -- and some of us do not think that the last option is -- amounts to informed consent.

DR. MURRAY: Okay.

PROFESSOR CAPRON: And it should not be included.

DR. MURRAY: So there will be a version without the (D) and a version with the (D) if that is how we do it.

PROFESSOR CAPRON: No.

(Simultaneous discussion.)

PROFESSOR CAPRON: The (D) will be listed and then there would be an asterisks --

DR. MURRAY: I understand. We are voting on --

(Simultaneous discussion.)

PROFESSOR CAPRON: -- would not go that far.

DR. MURRAY: Okay. All right. Not a problem.

MS. KRAMER: But, Tom, a point of information.

DR. MURRAY: Yes.

MS. KRAMER: I am just -- I am not sure thinking back -- does there need to be another position and that would be to give consent for the use of their samples for research purposes that maintains the links for certain specified kinds of research. What happened to that?

PROFESSOR CAPRON: I think you are right. We have a (D) but actually it comes in sequence earlier.

MS. KRAMER: Right. It comes earlier but that used to be --

(Simultaneous discussion.)

DR. MURRAY: I can say one problem I have with the current number 17 is that it looks like this is the set -- that these are the necessary but only permitted sets. The language we have is that these are the only three things you can recommend. I am not sure we want to put IRB's in that kind of straight jacket and I would hope that the people who were drafting it will take that into account.

PROFESSOR CAPRON: That is a good point.

DR. SHAPIRO: We will redraft 17. Let's not worry about it now.

DR. MURRAY: Okay. And you will give us something to choose among. I do not care how --

PROFESSOR CAPRON: I think Bette is quite right. We had extensive discussions from people and there it makes much more sense to me for someone to say, yes, if you want to do further breast cancer research on my

sample, this is my disease, I understand it, you know, I want to see it conquered, go ahead, and you do not have to come back to me with every study. That makes more sense than just this anything you could find here any time in the future with any possible clinical, social, discriminatory effects, go ahead.

MS. KRAMER: Now I have one more question. I am sorry. It is not clear to me this whole page 40, whether this applies equally in the clinical setting, in the research setting.

DR. MURRAY: Both.

(Simultaneous discussion.)

MS. KRAMER: All of this is applicable to both so even -- so if somebody is going in for surgery they are going to get confronted with --

PROFESSOR CAPRON: Right.

MS. KRAMER: Okay.

PROFESSOR CAPRON: Fifteen speaks to the clinical because the idea there is to make sure you unlink --

MS. KRAMER: I understand that.

(Simultaneous discussion.)

MS. KRAMER: But then having made that clear you are nonetheless -- 17 is going to come into play. Sixteen and 17 both.

DR. MURRAY: Let's do one at a time. Seventeen, yes.

MS. KRAMER: Okay.

DR. MURRAY: I do not want us to -- I want to -- okay. I am appointing a drafting team. I am asking -- I am volunteering you for a drafting team. Harold is willing to sort of lead this effort. I would like Bette to be on this team. Alta is not here.

PROFESSOR CAPRON: Pick her.

DR. MURRAY: I would like her to be on the team. It is an appropriate punishment. I do not mean that quite in those terms. But that is what I would like to have and if anyone else wishes to be involved in this that is fine. Please let Harold know. Harold is going to lead this one. Thank you very much.

PROFESSOR CAPRON: Tom, could I offer some clarification on 18 where there was a question before because I think the language here is simply mistaken and that is what the origin is --

DR. MURRAY: Sure.

PROFESSOR CAPRON: It is not medical records. The citation is incorrect.

It should say 45CFR46.116(a)(5) and the language of that section is that -- and the introduction is basic elements of informed consent, the consent form must provide -- and point number five says a statement describing the extent, if any, to which the confidentiality of records identifying the subject will be maintained. The suggestion to me there is research records. The records generated by this research project. It is not medical records.

DR. MURRAY: Well, we are on 18. Shall we just stick with it and see if we agree with that then?

PROFESSOR CAPRON: I do not know why we need that because we are not saying anything anymore than is already in that section.

DR. MURRAY: Okay. So this adds nothing new to the requirements already --

PROFESSOR CAPRON: That is what I would think.

DR. MURRAY: Do we agree on that? Does anyone

feel differently?

DR. MIIKE: I briefly mentioned it to Alta and she said she did not know why it was there so it was not her doing.

DR. MURRAY: Okay. Any other comment? We are just going to drop this?

PROFESSOR CAPRON: Whoever put that in, if they had something in the transcript that led you to that maybe there was another idea that it was supposed to lead to and we do not want to lose that.

DR. MURRAY: Eric?

DR. MESLIN: The reason for suggesting it was that while the disclosure in the regs simply operationalize it and telling something what practices are going to be in place, it appears from discussion that commissioners have had that there are not absolute guarantees of protection and that either additional sensitivity to this issue is what is meant by that and there obviously is no explanatory text. There could be if you thought it was appropriate.

But the additional "and any difficulties associated with maintaining such protections" is an

additional step beyond simply saying this is what we are planning to do, which is all you have to do to satisfy the regulatory requirement.

It may be that you should be telling people, you know what, it is really unlikely, in fact, that we can offer any guarantee of confidentiality because once it goes into GenBank or once it goes into libraries around the world there is absolutely no way of offering guarantees and you should not enter a study with the mistaken impression that a general guarantee of confidentiality will be provided. That is the --

PROFESSOR CAPRON: I actually -- I think that since the existing regulation does not say guarantee confidentiality, it itself says the extent, if any -- if any, to which confidentiality will be maintained. That strikes me as saying the same thing. If you are turning it into GenBank or whatever -- yes.

DR. MURRAY: Do we have a decision to be made on 18?

PROFESSOR CAPRON: Strike it.

DR. SHAPIRO: Take it out.

DR. MURRAY: Is the consensus to strike it?

The consensus is to strike it.

DR. SHAPIRO: I think I am quite satisfied to strike it. I am not concerned with that as a recommendation. I do think in the -- I mean, I am increasingly concerned with the typically maintaining confidentiality of records, not people's intention but just the difficulty of it all. And I think our report has to reflect that and need not have 18. I do not think that adds -- I agree with that. But we are going to have to develop more text than we now have, which just deals with the problem of this increased difficulty.

PROFESSOR CAPRON: I must have missed it. Did this come out of the Princeton meeting, Kathi? This decision that we were moving all the commentary up front and doing the recommendations -- I found the format of the capacity report, the impaired capacity report, quite satisfactory where we followed it, a recommendation with the discussion.

And Bernie's comments about 17 it seemed to me were right along that line. We have got to explain -- after you say this you have got to explain what the intention is and whatever. So -- I know this sounds like

saying to the staff undo what you just did. I do not recall the decision being made but obviously I was not listening to the point or something where you were told move all that up and it may be principally Larry who has just left the room who likes the recommendations without any kind of --

DR. MURRAY: He does not want to see them that way.

(Simultaneous discussion.)

PROFESSOR CAPRON: It comes to mind, Mr. Chairman, precisely because earlier on we do have a statement about investigators talking about how they will protect the inadvertent release. And commentary on that would be a very appropriate point to say this is a particular point of sensitivity about these kinds of records and, of course, once having done that that provides a basis for fulfilling the obligation under 116(a)(5) to inform the subject and you do not need a recommendation but it is right there in the text at the point where you would be thinking about it.

DR. SHAPIRO: At the very least as we decided yesterday we would have running commentary and whether we

actually go all the way back to the model that was used in the capacity report is an open issue. I think we just have to think about it.

PROFESSOR CAPRON: Well, the capacity report, as I recall, had some material in that recommendation chapter that was sort of general conclusions and then we got to the recommendations but we were able to --

DR. SHAPIRO: Correct.

DR. MURRAY: Diane has been waiting to be recognized.

DR. SCOTT-JONES: One of the points I wanted to make has just been made and that is that we had agreed to add explanatory language when we were discussing this yesterday and I would also suggest that we highlight the distinction between the sections that focus on already existing samples versus prospective samples because Harold explained that a while ago in response to a comment that I had made. I can see that it is there but it is really not highlighted in the words used in headings to make it clearer that you are switching to talk about a different category of research.

I would also urge us to be careful in language

used in headings such as informed consent versus consent to make it clear that we are not somehow switching categories of things going from consenting and leaving the idea of informed consent.

DR. SHAPIRO: I think that is helpful.

DR. MURRAY: Kathi had --

DR. SHAPIRO: I am sorry.

DR. MURRAY: I am sorry, Harold. Kathi has been wanting to say something.

DR. SHAPIRO: Go ahead.

DR. MURRAY: Why don't you finish?

DR. SHAPIRO: I think the issue of trying to -- in the way we set out this report to make it easy for someone who wants to know what to do with existing samples or previously collected samples, what to do to be able to go directly to that which concerns them is going to be a requirement when we get down to the final part of the report, so I think that is an important issue to do as opposed to those who are going to collect prospective samples. But just how we merge this all together I am not entirely sure but I think it is a good point.

DR. MURRAY: Kathi?

DR. HANNA: If anyone has a good idea about how to organize these recommendations into the two categories I would love to hear it. It is -- when you sit down and try and do it, it becomes very, very difficult. Especially when you are dealing with consent because the commission decided that the consent issues should be the same whether it is a brand new consent on a sample that you are collecting today or it is a reconsent and you are going back to someone to use their stored sample and you are getting a consent.

The commission decided the components in the nature of that consent should be the same.

So where do we put those issues? Do we put them under --

DR. MURRAY: Okay. I have an idea --

DR. HANNA: There are some things that fall plainly into one category or the other. There is a lot of overlap. It is a real writing challenge to try -- we can be very redundant and very repetitive in the chapter and that --

DR. MURRAY: May I --

DR. HANNA: -- we can do that.

DR. MURRAY: May I make a proposal that I began to float yesterday and I am going to propose it again today. Namely that we do it -- we develop it in the actual body of the chapter in whatever way makes the most sense recognizing that we will then want to gather probably at the end of the chapter and then prepare sort of information sheets of different sets.

What if you are gathering new samples, what recommendations, and just list the recommendations and refer them back to the text. What if you are using samples that have been collected before the effective date of the report's implementation? You would list the -- maybe it would be repetitive but you will list them again. What if you are an IRB, what recommendations are relevant? The list goes.

And we simply have a collection that people can -- rather than try and -- you know -- take a multidimensional problem and cram it into a linear form, just acknowledge the fact that it is multidimensional, that it is reiterative and prepare a set of information sheets directed to sort of each question or questioner who might approach the report. That is my proposal.

Harold, were you going to make a proposal also?

DR. SHAPIRO: No. That is fine.

DR. MURRAY: Okay. All right.

Why don't we look quickly at the recommendations that may not be controversial. I say that with great trepidation.

Let's look at 11. Eric has praised many of these for their clarity and simplicity. I agree. Eleven says consent to the research use of human biological materials should be obtained separately from consent to clinical procedures.

We have two questions. One is the meaning of this on target? Who thinks -- does everybody agree that this is on target?

We have a separate question. Should we combine it with other recommendations per Jim's earlier suggestion? Eric seemed to believe that we should not, that they have a kind of clarity that is worth retaining as separate recommendations. I confess initially I favor Eric's idea. But let me --

PROFESSOR CAPRON: We want to say informed

consent, right?

DR. MURRAY: Informed consent.

DR. SHAPIRO: That changes it.

DR. MURRAY: Bernie and then Larry.

DR. LO: I just think again that it would help to have a couple of sentences at least to explain what we mean by separate.

DR. MURRAY: In the recommendation or in the text that follows?

DR. LO: In the text that follows.

DR. MURRAY: That is fine. That -- we are going to do that, Bernie, I think. Yes, I agree with that sentiment completely. So there will be explanatory text rather than simply a list of recommendations in the body of the report. Right?

Carol -- I am sorry. Diane?

DR. SCOTT-JONES: It seems to me that number 15 follows from number 11 and it is not clear to me that 15 is more relevant to the form or document itself than to the process. It just seems to me that it would read more smoothly if you put the point in number 15 with number 11.

DR. MURRAY: I like that idea.

PROFESSOR CAPRON: You mean immediately after.

DR. SCOTT-JONES: Yes.

DR. MURRAY: Or have it be part of -- combine them as one --

(Simultaneous discussion.)

DR. SCOTT-JONES: Either way.

DR. CASSELL: Twelve is when seeking consent.

MS. KRAMER: I do not think breaking it into a section on process and a section on --

(Simultaneous discussion.)

DR. MURRAY: We are not going to do that.

MS. KRAMER: Right.

DR. MURRAY: Does everyone agree with that?

MS. KRAMER: Yes.

DR. MURRAY: We are not going to separate --

MS. KRAMER: Yes.

(Simultaneous discussion.)

DR. MURRAY: Informed consent is one section. We now have it -- we have 11, granted the numbering is going to change, but what is currently in 15 will now follow 11 but it will follow it as a separate recommendation. Does everyone agree to that?

Does 15 -- does the language in 15 more or less capture what you want to say?

DR. CASSELL: Yes.

DR. MURRAY: It does it pretty well?

MS. KRAMER: Yes.

(Simultaneous discussion.)

DR. MURRAY: We know that. Yes. I have got that in my notes, too. Okay.

What about the current 12? Does that capture our intent?

MS. KRAMER: I would propose that 16 should follow after -- should be moved up right behind what is now 15 that would become 12.

DR. MURRAY: I am sorry. Can we just focus on the current 12?

MS. KRAMER: All right.

DR. MURRAY: We will deal with the order of subsequent ones later.

DR. BACKLAR: It ought to be --

(Simultaneous discussion.)

DR. BACKLAR: -- 16 goes right under 15 --

MS. KRAMER: Right.

DR. BACKLAR: -- better to have 12 come after 16.

DR. SCOTT-JONES: I agree. That was my point.

DR. MURRAY: Okay. I will stand corrected on that.

Let's look at 16 then because that is proposed to be the next in order. It probably should say persons whose tissues -- whose biological materials are being requested. Otherwise this is a generic thing to all persons but I captures well. Does everyone agree with the sense of 16?

Larry?

DR. MIIKE: Just to get back to 12, you know, the way it is phrased it is about a specific research protocol. We are talking about a general -- the general consent document. So it really does not quite fit in.

DR. MURRAY: All right. We are on 16 right now.

DR. MIIKE: I understand that but we passed over 12.

DR. MURRAY: No.

DR. SCOTT-JONES: No.

DR. MURRAY: We are going back to 12.

DR. GREIDER: It goes 11, 15, 16, 12.

DR. MURRAY: We are going back to 12. We have not finished with 12.

DR. MIIKE: Well, I do not argue. We need to reorder these things. They obviously need to be --

DR. MURRAY: Yes. We are just -- I wanted to do 12. I was overruled and that is fine. But we are looking at 16 right now to see if 16 captures what we want to say.

MR. HOLTZMAN: Tom?

DR. MURRAY: Yes, Steve.

MR. HOLTZMAN: If we are envisaging a consent to a specific research protocol with no broad future consent it is not clear to me why you would be talking about this. On the other hand if you are envisaging a general consent to future research, whether with or without opt, whether linked or unlinked, et cetera, et cetera, then you start to say whether or not there is a moral obligation.

At least speaking from my own personal work from my companies we do go into these kinds of disclosures

because we are seeking broad consent beyond the specific protocol the right to use the samples in a coded fashion in future research of all different types and, therefore, we do disclose these things.

DR. MURRAY: Any reaction to what Steve just said?

Eric?

DR. CASSELL: Well, I agree with him. I do not see what that adds. If you have a proposal on the table that somebody is going to consent to that covers the situation. It is in there if you are asking for broad and future consent I do not see what it has got to do -- we have agreed already that is in question. On the other hand, since we have the option going there -- remember we are going to provide an option, we have not finished -- we had not closed that discussion about future use, right.

DR. MURRAY: Carol?

DR. GREIDER: I do not read 12 that way. I do not see why this does not make sense in the case of --

DR. CASSELL: I am sorry.

DR. MURRAY: We are skipping around. We are -- I think we are reading 16 right now, aren't we?

DR. CASSELL: We are on 16.

DR. GREIDER: Oh, we are on 16.

DR. MURRAY: Yes.

DR. GREIDER: I am sorry.

DR. CASSELL: What does that add -- why are you doing that aside to show what a wonderful thing research is?

DR. MURRAY: Well, I thought it was in there to warn people that there might be --

DR. _____: That is how I took it.

DR. MURRAY: -- implications that they should contemplate before agreeing particularly if you are asking for a more general consent to the use of tissues.

Diane and then Bette.

DR. SCOTT-JONES: I was not sure what Eric and Steve were objecting to about it. Is it just that the language is too broad and thus not meaningful or useful?

DR. CASSELL: Yes. Here I am giving this consent, I am about to get operated on and have a piece of breast tissue removed. I am giving a consent to have my tissues used for this and now a part of it says I should be -- I should realize that my tissue may have medical,

cultural, political or economic -- you know, what I am doing that for? That is wonderful. I did not know my breast tissue had such meaning in the world.

DR. MURRAY: But it always has, Eric.

MR. HOLTZMAN: I think very simply -- I think the notion of 16 is if we have the recommendations that are --

(Simultaneous discussion.)

MR. HOLTZMAN: -- call them blanket consents, all right, then I think the sense here is that we have an obligation to inform people that that blanket consent could involve many different kinds of research, some of which they may find objectionable.

Now if we have got opt out as a requirement, all right, the need for that kind of probably goes away but we were envisaging that opt out would not be there.

DR. BACKLAR: But then wouldn't this have to go into maybe 17? Maybe this is not a separate one. Maybe this is where you have all this list of possible options and you need a little education in there.

DR. GREIDER: Sixteen goes with 17.

DR. MURRAY: Larry, and Bernie.

DR. MIIKE: Well, I do not really think so because 17 really gives you the choices.

DR. MURRAY: Yes.

DR. MIIKE: But that is a minor issue. I do not think we need 16 because we are talking about an informed consent process to me it is implicit there. If you are going to have an informed consent process you are going to talk about these kinds of things and I do not think we need to list it as a specific recommendation.

DR. SHAPIRO: I agree.

DR. MURRAY: With full awareness of the possibility that things we do in fatigue and haste today may come back and bite us next month I think that is an excellent suggestion and I see others who feel the same way.

Is there a general -- Bernie, did you want to speak because I am going to --

DR. LO: No, I would suggest we not make a recommendation and put it in text that is right near the recommendation.

DR. MURRAY: All right.

DR. LO: I think it does capture an important

point that these are --

(Simultaneous discussion.)

DR. LO: -- you are supposed to do it. I do not think the quality of these discussions is anywhere near as good as the quality of discussions --

(Simultaneous discussion.)

DR. LO: -- he really tries to go into it to try and make that choice of options in 17 meaningful is important to try and capture. I also think this is a little too neutral. But we are not saying -- I mean, Eric and others may feel, oh, this is great. But I think what we are trying to say is, look, there may be some stuff down the pike that we cannot predict that you may have some objections to. Make sure you really understand what you are signing up for.

DR. MURRAY: Larry's proposal is to demote what is currently recommendation 16 to explanatory text. Can I ask a quick straw poll? All in favor of that proposal?

(A show of hands.)

DR. MURRAY: Any opposed to that proposal?

DR. SCOTT-JONES: A modification.

DR. MURRAY: Diane?

DR. SCOTT-JONES: I think if it is removed from the recommendation to the text it should incorporate Bernie's suggestion and that is that it not be so neutral but that it point out that there might possibly be some uses to which persons might object so to be more straightforward about the concern.

DR. MURRAY: Bette, and then we are going to do another straw poll.

MS. KRAMER: Okay. I would also like to see it -- even if it is text as opposed to recommendation -- included in the consent process.

DR. SCOTT-JONES: We agreed to that. We already agreed --

MS. KRAMER: Right. The language -- I am just saying that if it -- if it gets eliminated as a recommendation and moved down to text that that text be included as a part of the process.

(Simultaneous discussion.)

DR. MURRAY: I am sorry. I have now lost the thread here.

DR. LO: I think what --

DR. MURRAY: Microphone, Bernie.

DR. LO: I mean, I think what we are saying is we would like to see this on the same page just not involved in text. Not moved to page three or four.

DR. MURRAY: Okay. So with the sort of provisions that Diane and Bette have just proposed who would be in favor of demoting 16 to text but keeping it as part of the explanatory text for this section?

(A show of hands.)

DR. MURRAY: All opposed?

(A show of hands.)

DR. MURRAY: Bette is opposed?

MS. KRAMER: Yes.

DR. MURRAY: You still want to keep it as a recommendation?

MS. KRAMER: Because I am just afraid it is going to get lost and I think when you go on later and ask people to give consent -- to consider giving consent in all these possible ways that it is important that they have that background.

DR. MURRAY: Okay. Why don't we see how it emerges in what I hope will be the next and final draft.

Diane?

DR. SCOTT-JONES: I want to make another comment that exists in this recommendation and some others. You mentioned the use of the word "persons." I think I remember that when we were doing the capacity report we agreed to a convention in which we would refer to persons as persons when the writing had the meaning that they were not already in a research project and that we would use the word subject when the writing had the sense of them already being in a research project, and we agreed to subjects over participants. I think we had quite a bit of discussion about persons, subjects and participants, and is that the convention here that we are using persons intentionally and we do not really need to change it?

DR. MURRAY: I think it is a very desirable thing that the committee retain a consistent use of whatever terms across reports. So let us do our best to see that that is observed. Does everyone agree that we should try to observe that?

DR. BACKLAR: And potential subjects.

(Simultaneous discussion.)

DR. MURRAY: All right. Good. What about the current 12?

DR. MIIKE: Again, as I say, it is out of place in that the subject matter itself is incorporated in what was old 16 because that is the kind of discussion one would have anyway about the concerns and risks.

DR. MURRAY: So what do you want us to do with this, Larry?

DR. MIIKE: Drop it.

MS. KRAMER: Drop it or incorporate it with what was 16?

DR. MIIKE: It is generally incorporated in this -- I mean, 16 is a very large category and you would include that.

DR. MURRAY: Arturo?

DR. BRITO: If we drop this, okay, we have already dropped nine, and Harold and I talked a little bit about this yesterday after the point I was trying to make, 19 talks about dissemination of results -- a plan for disseminating results that may involve groups.

We do not have anywhere in the design then where you have an identifiable sample. You have the word

unidentifiable sample but not identifiable samples. So by dropping it here you are going to be left out in the design process, in the consent process an investigator in the design -- so somewhere in here we need to put something about when you have an identifiable sample and an identifiable group or a specific group that could be affected, they need to be protected somehow.

DR. MURRAY: Because the issue of group -- potential harm to groups is a significant one in this particular report in the case of biological materials and especially genetic research, I agree with Arturo that we should -- and probably -- yes, IRB's should think of it but it should be -- it is sufficiently uncommon for IRB's to think about such matters and sufficiently cogent to this report that we should list it as a separate recommendation. So I want to propose keeping something like 12 in. It does not have to be in this spot.

DR. MIIKE: That is all I said.

DR. MURRAY: Okay.

DR. MIIKE: I thought the discussion was that we might even actually have a section of recommendations on group issues.

DR. MURRAY: Okay. Would you be happy with that, Arturo?

DR. BRITO: That is fine. And one very minor point just for -- you are changing identified group to a specific group. It gets very confusing if you put in different section samples identifiable and unidentifiable.

DR. MURRAY: That is a good point.

DR. BRITO: It poses a risk to a specific group because that would be identified. I mean, obviously it is identified.

(Simultaneous discussion.)

DR. HANNA: I cannot remember who -- which one of the commissioners was concerned that the issue is that the group can be identified before the research is done. Groups can emerge out of the research which obviously you cannot anticipate in any way. So people wanted to somehow convey the notion that this obviously only applies for research where you know you are dealing with a group. So you can use a different word than identify but --

PROFESSOR CAPRON: That is what I thought Arturo was suggesting.

DR. BRITO: Right, that is what I was saying.

(Simultaneous discussion.)

PROFESSOR CAPRON: Identified, we are using it so much in the individual --

DR. GREIDER: Existing is what you want to say.

DR. MURRAY: I want to make a proposal --

(Simultaneous discussion.)

DR. MURRAY: I want to make a proposal --

(Simultaneous discussion.)

DR. MURRAY: I want to make a proposal that Larry and Arturo would please constitute the group. I do not think this is going to be a major job. I am going to give two --

(Simultaneous discussion.)

DR. MURRAY: I want to give you a dual assignment. One is to just make sure we have got this right and we say it right. The language is -- and also what -- how to group recommendations pertaining to groups and group harms. Okay. So I think I am asking for two things.

PROFESSOR CAPRON: In an identifiable way.

DR. MURRAY: In an identifiable way. An

accountable way. That you would give us a redrafting of what is currently 12 and also that you might indicate what other recommendations might be pulled out to be in a section on groups. Is that -- Larry, thank you very much.

(Simultaneous discussion.)

DR. MURRAY: Does one of you volunteer to be the honcho of this little drafting group? Arturo, would you be the honcho? Okay. Arturo is going to be the honcho. Thank you.

Would it be all right, Harold, if we go to 12:30 or do you think we -- feel we --

DR. SHAPIRO: Yes, I think we should adjourn in ten minutes so why don't we just go on. There is no reason -- Tom has to leave. Let me just say for a moment, Tom, I think, has to leave at 12:30. I do not know other's schedules. I am hoping that after we break for lunch there will be some number of us to reassemble because I want to revisit some issues on the stem cell issue that came up yesterday. At least have some discussion. There is probably not enough of us here to reach any conclusion but just a discussion for those of you who are able to stay.

What are the schedules around the table incidently?

DR. _____: I can stay until 2:30.

DR. _____: 2:00.

DR. _____: 2:00

DR. BACKLAR: I can stay until 2:30.

DR. SHAPIRO: Okay. So we will have -- maybe if we break for three-quarters of an hour we can have an hour or so -- an hour, hour-and-a-half of discussion. Okay.

Tom?

DR. MURRAY: I apologize.

Yes, Bernie?

DR. LO: Can I just ask sort of an agenda point? We have never talked about 23 and 24, sort of the blanket things that have to do with federal and state privacy legislation that John Fanning talked about yesterday. Do we want to try and say something about that before we all dissolve or do we want to put that off --

DR. MURRAY: Well, would you -- I would like to -- how far can we get in ten minutes? We have one consent recommendation left by my count, which is number

14. Can we get a quick --

DR. MIIKE: By my recollection we have made this moot because of our additional vote on the consent process. We now have an opt out provision.

DR. SCOTT-JONES: Right.

DR. MURRAY: Do the proponents of the opt out provision think that -- agree with that?

DR. LO: I read this to be something different. I read that in this situation where the researcher wants to go back to the subject to inform them of results that may be a preliminary interim result --

DR. CASSELL: New consent.

DR. LO: No, no, I can say here that I do not want to -- I do not want you ever to talk to me again -- oh, I am sorry. Forget it --

(Simultaneous discussion.)

DR. MURRAY: Could I ask the folks who are redrafting 17 to reflect on Larry's observation and see whether, in fact, it is made moot and if it is then that shall be the ruling. If there is a feeling there was still some purpose served by something like 14 then please give us a redraft of it.

Larry, is that acceptable to you?

Thank you.

All right. What is your pleasure? We have 19, 20 -- we have 19 --

DR. GREIDER: Nineteen does not exist anymore.

DR. MURRAY: Nineteen is gone. Nineteen does not exist anymore.

DR. GREIDER: I think we got rid of it.

DR. MURRAY: Carol thinks we got rid of 19 yesterday.

DR. LO: No, no.

(Simultaneous discussion.)

DR. MURRAY: I do not think so.

DR. _____: I thought it was misplaced.

DR. _____: What we are going to do now is group -- group the category.

DR. MURRAY: Any comments on 19 since its existence is?

MS. KRAMER: I do not think we reached any resolution on that. I think that we felt as though that had reference to family so we had dealt with groups earlier and that we had not talked about families and we

saw 19 as possibly encompassing families. I just do not think we came to a resolution on that.

DR. BRITO: Tom, can I give a synopsis because I think --

DR. MURRAY: Yes.

DR. BRITO: -- after talking to Harold I think I got it now. Nineteen, when you go to disseminate information it does include families because it says for harms to individuals or groups who are related to the same source by kinship or other significant associations.

MS. KRAMER: Right.

DR. BRITO: The question we had yesterday was about the design --

(Simultaneous discussion.)

DR. BRITO: Larry and I will take care of that with the addition -- whether in the consent process or design, where families are not quite as relevant, only groups are more relevant in the design and you need to include unidentified and identifiable samples. So I think we will take care of that.

DR. MURRAY: So are you offering to also rework 19 if necessary?

DR. BRITO: No. I think 19 can stand as it is with the addition of the one that takes care of it within the design and/or consent process for groups.

DR. MURRAY: Steve, and then Trish.

MR. HOLTZMAN: So let's just focus on the issue of the dissemination of the results, not the design. When one is talking about kinship there are guidelines that we could reference for how to deal with pedigrees to disguise. Okay. But I think there had -- if I read this literally you should include provisions to control, reduce or eliminate. And I think Harold has made the point that there are kinds of research which might take place -- now I am talking about groups, not kinship -- where it is in the nature of the research that you cannot control, you cannot reduce, you cannot eliminate.

And are we here saying that at least by implication you should not disseminate those results? And if we are not saying that I think we need to word this something to the effect of “to the extent possible to control, reduce or eliminate.”

DR. SHAPIRO: Well, I do not have the words. I am not sure “to the extent possible” does it but I agree

with the sentiment you are proposing. This is not an attempt to try to sort of censor or somehow control or -- it is an attempt to ask people if it is not inconsistent with their own work that they should not do -- make every effort to do this and that is the sense of it that I have. I do not know exactly what the right words are. I agree with you.

MR. HOLTZMAN: Okay.

DR. MURRAY: Trish?

DR. BACKLAR: I think there is also something else that when you are going through this you may want to do what we did in the capacity report and that is to cross reference some of these recommendations --

DR. MURRAY: Right. No problem.

DR. BACKLAR: It seems very obvious but we have not mentioned it and I just wanted to state it.

DR. MURRAY: Anything else on 19? I did not hear any dissent from Steve's request for clarification. Very well. We shall try and incorporate that in the new 19. I do not think we need to appoint a drafting body for that.

Twenty?

DR. CASSELL: Do we have to have this? I mean, isn't this a part of all -- it is a routine matter now and you --

(Simultaneous discussion.)

DR. CASSELL: -- have to put it in?

(Simultaneous discussion.)

DR. MURRAY: It is practice but it is not routine.

PROFESSOR CAPRON: The Council of Biology Editors has had a statement on this for about 20 years but studies that have been done indicate that many of the editors whose journals were members of the Council of Biology are unaware of the policy and they will be unaware of our report.

DR. SHAPIRO: It is like university rules and regulations.

PROFESSOR CAPRON: Our report, however, will be obviously indelibly etched on their --

(Simultaneous discussion.)

DR. MURRAY: Yes, Diane and Steve?

DR. SCOTT-JONES: I would like to say with a

great deal of pride that we do this in the journal that I edit.

(Applause.)

DR. SCOTT-JONES: You have to send in a revised cover letter stating that you have treated your participants fairly in your study. So some people do this.

(Simultaneous discussion.)

DR. MURRAY: Steve?

MR. HOLTZMAN: So let me ask a question. This is a pure question. All right. If your study is not subject, it involves human subjects but it is not subject to the regulation because it is privately sponsored in a private institution, would you write to the editor that you were doing it in compliance?

(Simultaneous discussion.)

DR. SHAPIRO: If you are in compliance then you are in compliance.

(Simultaneous discussion.)

DR. SHAPIRO: If you are not in compliance, shame on you.

PROFESSOR CAPRON: If I am a biology editor

getting that I would say, "Although you were not required to follow the rules, did you follow them?" If you say, "No," I will say, "I will not publish your research."

MR. HOLTZMAN: Well, you see that was the question. So the recommendation is effectively, right, that even though you were not subject to the reg, you did not act as if you were subject to the reg, we are suggesting your stuff should not get published.

DR. CASSELL: That is correct.

DR. MURRAY: I think that is --

(Simultaneous discussion.)

DR. MURRAY: Yes. I say with some embarrassment as the new --

(Simultaneous discussion.)

DR. MURRAY: -- Hastings Center report, I do not know if we have that policy for our own articles and we publish occasional empirical research these days but I will raise that question when I return.

MR. HOLTZMAN: So that we are not yet recommending --

DR. CASSELL: Change the word "compliance" to “in accordance with.”

DR. MURRAY: Yes, I like that. Is that different? I appoint Eric Cassell as a one person drafting team.

DR. CASSELL: All this time. I thought I was going to get away --

DR. MURRAY: To make sure that 20 is good, Eric.

Okay, Eric?

DR. CASSELL: All you have to do is -- I just told you to change it to “in accordance with.

DR. MURRAY: Okay. That is fine but you are in charge.

Twenty-one?

MR. HOLTZMAN: That does not answer my question.

(Simultaneous discussion.)

DR. SHAPIRO: I would interpret 20 -- regardless of anyone might feel, 20 does not tell editors what to publish and not to publish. It does not say that in my opinion the way this is “whether.” So you could read “whether or whether or not so I do not see any difference, right. And now we may or may not wish to say

this is an absolute bar to publication. That is another issue. That is not what this says.

PROFESSOR CAPRON: We do not have that power.

DR. SHAPIRO: So I just want to point out this is not saying -- we are not giving instructions to editors other than to find out whether your research has been conducted -- and then what they do is their business. According to this recommendation. I am not arguing on one side or the other.

DR. MURRAY: That is correct.

(Simultaneous discussion.)

DR. SHAPIRO: That is what this recommendation says.

DR. CASSELL: You could not do anything else.

PROFESSOR CAPRON: But I think if we are going to do that then we should cite the policy of the Council of Biology Editors that results ought not to be published but -- and this is a statement of disclosure.

DR. SHAPIRO: Right, this is disclosure.

DR. MURRAY: I think that would be an important thing to cite in the context of this recommendation. Agreed.

Twenty-one?

DR. SHAPIRO: We now have about two minutes left.

DR. MURRAY: There you go. We have got about 30 seconds per recommendation. How do you want to use it, Harold?

DR. SHAPIRO: I think maybe we could ask people if they have some judgments on 23 and 24 because I, first of all, think that 22 is not very controversial because those are here now with some explanatory notes.

PROFESSOR CAPRON: I move to strike 23.

DR. MURRAY: There is a move to strike 23.

PROFESSOR CAPRON: There will be plenty of people arguing that there are undue burdens here and we do not have to make that --

DR. SHAPIRO: I am sorry. What is the argument?

PROFESSOR CAPRON: I do not see what this adds. I think, throughout, our concern ought to be towards the protection of human subjects and this is -- sounds to me like something which will be adequately argued. Any additional burdens will be adequately brought

forward and -- this is either a truism or we are lobbying on the side of wait a second, we have said all these things but let's not unduly burden this progress of science. Are we saying that the recommendations offer -- the protections -- little additional benefit to individual patients or to society?

DR. MIIKE: I agree with Alex. This thing is so tangential to what we have been doing.

DR. SCOTT-JONES: I agree.

DR. MIIKE: This sort of sticks out.

DR. MURRAY: Steve?

MR. HOLTZMAN: Well, I will offer a dissent. All right. But I will not push it. Alex has articulated his position before and this goes to the heart of the concept of what this commission is about and what its role is. Alex puts it forth as offering a counter balance to a research community who "effectively" lobbies for a certain kind of unfettered research and, therefore, that the role of an ethics commission is a counter-balance to that.

There is another concept of an ethics commission, which is weighing those concerns on both sides and trying to come up with the conclusions that give voice

to both in an appropriate balance. From that perspective such a statement as this, putting aside the specific words, would be viewed in that context. That is more in line with my concept of this commission but I do not want to push it here.

PROFESSOR CAPRON: I would agree if we had any decision making power that balance would be necessary but we are just putting some weight on a scale for other people who have all the decision making power.

DR. SHAPIRO: My own view, Tom, is that we have a lot to do here and if people do not feel that 23 and 24 are something that we need to express ourselves on we do not want to spend time but I would like to hear what people feel.

DR. MURRAY: We have Trish and Carol.

DR. BACKLAR: I actually think that 24 is -- somewhere we would want to say there is some uniformity. I think this is not unimportant.

DR. MURRAY: Carol?

DR. GREIDER: Twenty-three and 24 have not come up a lot in our previous discussions and I would feel uncomfortable striking them or leaving them in at this

stage when we have not really had a chance to consider them one way or the other. So I do not feel comfortable doing either one of those things.

PROFESSOR CAPRON: I think that is actually -- I would agree with that.

DR. MURRAY: That is wise. My judgment is that is a wise course. We should not hastily vote them up or down.

DR. GREIDER: But perhaps more explanatory material along the lines before the next meeting would help.

PROFESSOR CAPRON: If we are going to do that, 24, it seems to me, mixes at least two concepts. There is the concept of interstate uniformity. There is the concept of -- and then there is the concept of uniformity among types of research. Those are very different arguments. I think interstate uniformity absolutely has everything going for it and consistency between federal and state provisions has everything going for it. I do not believe that we have to have absolutely identical schemes for different types of research as we heard yesterday.

In the context of drafting the criminal statute the Department of Health and Human Services was taking a conservative view on what conduct would be prohibited in terms of -- and drawing lines around, for example, coded data being treated as unidentified and so forth. I can understand that because criminal statutes deter more behavior than they are intended to and the risk of the penalty there being applied to someone who is -- the egregious nature of what they have done is very mild.

I think that there are good reasons for treating our recommendations about regulations, which are not criminal in the human subjects protection area where we are talking prospectively about the design of research involving materials which are at the moment still in a different category than paper records, there would -- there is every good reason to think that there is some need for some special rules about these and they do not have to be identical to Medicare records.

DR. MIIKE: Just one comment. My view is that we are trying to reach closure on this report and if we start talking about this we are never going to reach closure. We are going to open up whole new areas. This

is not the time to add these kinds of things.

DR. MURRAY: Can I suggest that we conduct further discussion about whether to have anything about these two issues or these two recommendations and the merits of particular ways of approaching them and carry it on in the list-serv rather than around the table?

DR. SHAPIRO: Sure because I think we are going to have to --

DR. MURRAY: Kathi?

DR. HANNA: Let me just get some clarification. In one of the previous chapters, four, we have probably about eight or nine pages on medical privacy issues. Are we to take it that the commission does not -- wants to be silent on these issues?

DR. MURRAY: No, we are going to carry this conversation out on the list-serv for the time being. We may decide not to address it --

(Simultaneous discussion.)

DR. HANNA: I am trying to find out do you need staff to get additional information, clarification, provide any other materials so that you can have an informed discussion on the list serve or --

PROFESSOR CAPRON: Remind us. Does that discussion that is in chapter four incorporate everything that we heard from Fanning yesterday?

DR. HANNA: No, we just heard it today and yesterday.

PROFESSOR CAPRON: I mean it was already on the record that the Secretary's recommendation --

(Simultaneous discussion.)

DR. MESLIN: The issues are included but there is no position that is taken.

PROFESSOR CAPRON: No, no position but I mean it is clear that there are recommendations and that we treat certain things in certain ways. And if we needed to address it and we were not going to say we are in total lock step and there would be some reason on our part to explain why we would be different?

DR. MESLIN: Yes.

PROFESSOR CAPRON: And that is, I think, what Tom is saying we need to flush out.

DR. MURRAY: We may choose, as Larry suggested, simply not to go there on this report.

DR. BACKLAR: I am concerned. I just wanted

to say one thing. Coming from --

DR. SHAPIRO: Use the microphone.

DR. BACKLAR: -- coming from a state where there are terrific fights going on about genetic research and privacy, I am urging us to have some clarification -- some attention paid to this. I hope it does not add too much burden but I know that people are going to be looking -- certainly from my state -- are going to be looking to this hoping to get some clarification and advice.

DR. SHAPIRO: Yes. We will have to follow this up in some way. It is not clear to me exactly what we will do but -- so we will just have to keep each other informed on this.

I think we will recess for now. For those of you who are able to rejoin us at 1:30 for a half an hour or three-quarters of an hour or whatever we can put together -- as a matter of fact, if we happen to show up here at 1:20 that will be even better. It will give us a little bit more time to address the other issues.

Thank you.

(Whereupon, at 12:35 p.m. a luncheon break was taken.)

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

DR. SHAPIRO: We just have really a very short session here this afternoon.

I think there is a number of us -- some of us have to leave at 2:00. The rest, I think, at 2:30. It is already twenty to 2:00 so we do not --

DR. BACKLAR: We will resolve everything.

DR. SHAPIRO: We will resolve everything. There is an optimistic outlook.

I wanted to -- I was reflecting on yesterday's conversation on the stem cell issue and I want to return to that. If you recall the framework for that we are using -- we were using in our discussion -- it really came from two sources.

On one of our own initiative so to speak at the Princeton meeting we began looking at this sequentially -- I think that is the word that is used -- or incrementally, whatever one wants to do, and we have tended to do it by the source of materials, fetal tissue, excess embryos, cloning or IVF specifically for making research embryos and so on. That was initiative kind of path we took at our initial meeting in Princeton and it is

also the path that was adopted by Professor Fletcher in his presentation to us yesterday.

Using the categories that he presented yesterday just as a shorthand for the moment he listed them in some kind of order, I think the way he felt, from the least sensitive to the most sensitive in some sense, or the least problematical to the most problematical, however one might look at it.

And it was a case one, two, three four you recall, starting with fetal tissue and excess embryos and so on.

And our discussion yesterday, the impression I got from listening to the discussion, was that most commissioners were really comfortable with cases one and two, that is we retain it and say that those are areas that would really clearly be appropriate for federal funding for the reasons which I will not try to repeat now.

My first question is that his actual recommendations to us had two parts. One to consider cases one and two carefully, which we have begun doing, but it had a second part of it with that recommendation.

Namely some relaxation of the embryo research ban so that at least using materials from these particular sources in one and two that there might be some limits and/or regulation and/or -- I mean, some structure of some kind which watched over this -- that that might be an appropriate thing for us to recommend.

Now here I am less clear about how commissioners felt. I went away with the kind of casual type of impression that we thought that -- the "we" meaning most of the opinion around the table -- was at least positively inclined in that direction although no one as asked to make up their minds. So that is my first question.

Eric?

DR. CASSELL: I have spent a rather pleasant hour in the middle of the night about this because --

THE REPORTER: Your microphone.

DR. CASSELL: -- because it seemed to me that, in fact, we as a commission or as commissioners did have a sense that categories one and two were acceptable and that, in fact, we thought that it might be all right to get stem cells from that and so forth but I also reflected

on the interchange that John and I had about moving off the way the embryo is presently conceived.

The thing that struck me was that as I reflected on it I was trying to figure out -- well, to go back a step, we had a little discussion about what is the moral status of the stem cell. I rather like the picture of the moral status of the stem cell. But much more difficult is what is the moral status of an embryo? Up until now from my reading and from what I hear the moral status of an embryo is as a person but that is a category and categories have moral status -- can have a moral status but that is not the end of it because, in fact, we deal with persons in the culture very differently.

I think that one of the things that we have to recognize is that we can accept categories one and two but that we are going to get into a fight about it with people who have very fixed positions unless we begin to show how that embryo, which you may represent as a person or a living thing or however you wish to see it, what, in fact, are the possibilities of its moral status. Is it like all persons or is it like disabled persons, or is it like terminal persons? All of them are somewhat different and

we treat them differently in society.

We may say I am a person just like you but that is only the beginning of the statement and not the end of it, of the definition.

I think we need some help with working through the idea of just what is it we are dealing with that we have accepted would be reasonable to obtain stem cells from. Just what is this object once we leave its biological definition which even then is not a single category. When we go to biology I take it, it is more than one category.

So I think we have some work to do in order to understand and in order to make clear to others why it is that we believe it is possible to posit a change in the use of embryos because there has been a change in what would result from stem cell research.

DR. SHAPIRO: Eric, Rachel and then Larry.

DR. MESLIN: I do not know if it is helpful but in your briefing book I know you have all seen the document that Andy Siegel from our staff produced. It may be useful in light of the conversation that we have had to revisit that memo and Andy is here and you could ask some

questions about it and where the five types of ethical issues were at least placed on the table. It was not a document that was arguing for any one of these at the exclusion of others as being any kind of moral basis for the report.

But I do not know, Eric, whether you thought that that would be useful --

DR. CASSELL: Where are you?

DR. MESLIN: -- the document itself. It is in the -- under the memo from the February 24th summary of some ethical issues in human stem cell research.

But something like that might be -- we might want to hear some feedback from you as to whether that type of approach would be useful.

DR. CASSELL: Yes.

DR. SHAPIRO: Rachel?

DR. LEVINSON: I would also like to encourage the commissioners to return to the 1994 report of the NIH Human Embryo Research Panel because they considered these issues. There were background papers and information that did go into some of these, and just not to reinvent the wheel, and use some of the -- at least see what their

thinking was, whether you agree with it or not.

DR. SHAPIRO: Larry and Bernie?

DR. MIIKE: Several things. One is that I understood John Fletcher to say that on case two we should consider not only the ethical use of the stem cells as they are from spare embryos but of embryo research itself.

What I think about that -- and I know we are going to have ample discussion -- I do not rule out the possibility that -- I do not rule out a scenario in which we are not copping out by saying that research on stem cells from those sources are okay but still feel uncomfortable about research per se on the embryo. I do not think it is a cop out on that issue and I think we can make a good ethical argument for that.

The second point is that I think Lori Knowles is -- you know, Alex had a little exchange with Lori Knowles yesterday about whether her conclusion that most of the countries saw the moral status of the embryo from the time of fertilization as -- Alex was asking was that an empirical judgment or analytical. I think my interpretation of what she was saying was that since people's concerns begin at that point in time that is why

the focus is on fertilization.

It does not necessarily mean that we all agree that the moral status of the embryo begins or is set by that point, just that is the earliest point in time.

Given that, and I think our overall -- I would guess our overall conclusion would be that whatever the means of creation, the moral status of the created fertilized egg or whatever you want to call the beginning embryo is the same.

So one factor we did not discuss yesterday was that to me then that intent counts and I think that is what John was getting at on the somatic cell nuclear transfer and we, by implication, meant that, too, in our cloning report where we focused on the use of somatic cell nuclear transfer. We were very concerned about the creation of the human being. We did not pass judgment at that time about the use of that technique for research purposes or whatever.

So I think those are the kinds of issues that we have to address.

DR. SHAPIRO: Bernie?

DR. LO: I want to address the point of John

Fletcher's suggestion that we revisit the whole topic of human embryo research as opposed to stem cell research.

I would like to very strongly discourage us from doing that. I think that right now we have opportunity to make a small but very significant change in policies regarding stem cell research as one example of human embryo research. The arguments for doing stem cell research are much, much stronger than the arguments for doing other types of human embryo research.

As a veteran of the 1994 panel, if you look at the other reasons to do human embryo research they have to do with fertility treatment, prenatal, preimplantation, genetic, diagnosis of genetic conditions, basic science understanding. Those just simply do not have the resonance with the public that the prospect of transplantation holds out. So that, if what we think has changed from 1994 is the prospect of therapeutic benefit via transplantation through stem cell research, we give all that up if we drag in other situations that are just very clearly distinguishable.

So I think that there will be ample time later to readdress that question. We do not have to settle it

all now. I view this like an appellate court that gets a case at hand and we can either write a very broad report or a very narrow report. I would rather we focus on the stem cell issue because I think that is where the arguments for changing public policy are the most cogent.

You know, the 1994 human embryo research report was not perfect, by all means, but it laid out there the arguments for allowing research on human embryos for a wide variety of purposes. That was not accepted and it did not even come close to getting, you know, through the first hurdle. A lot has changed since then or a lot has not changed and I would hate for us to put forth a report that is intellectually satisfactory but just has zero impact on policy.

I think we should be much more modest and say what is the first step we can take, and if we can do that someone else may take the second step. If we try to take five steps now the risk is we lose and we do not move.

DR. SHAPIRO: Carol, and then Eric.

DR. GREIDER: I would just like to get a little bit of clarification. I thought that I understood what we were discussing yesterday when we talked about

case one and case two so let me just at least pose this initially as a question to you, Harold.

So the way I understood case one and case two was derivation of stem cells from fetal tissue or from embryo tissue and if I understand that correctly then case two would by definition be some form -- at least some form of embryo research because you are deriving -- you are doing something.

DR. SHAPIRO: Right.

DR. GREIDER: And so I do not see how one can then separately say are we going to say something about embryo research. So I am just a little bit confused about that issue.

DR. MIIKE: Case one is -- you did it correctly.

DR. GREIDER: Case one is derivation of stem cells from fetal tissue.

DR. MIIKE: Period.

DR. GREIDER: Case two is derivation of stem cells from embryo tissue.

(Simultaneous discussion.)

DR. CASSELL: Excess embryos.

DR. GREIDER: From embryos. Derivation. I am stressing the word "derivation" because I did not think that we were just talking about already extant cells that came from these tissues. That is what I want to distinguish from my case 0.5 yesterday.

DR. SHAPIRO: I think --

DR. GREIDER: And so are we talking about derivation or extant cells?

DR. CASSELL: Derivation.

DR. SHAPIRO: Derivation.

DR. BACKLAR: Derivation.

DR. SHAPIRO: We decided that yesterday.

DR. GREIDER: Okay.

DR. SHAPIRO: Derivation. The issue -- a separate issue, if there is one and if we want to address it or not that I was trying to just see where people stood, was we agreed, if I understand it, or at least intended to agree or moving towards agreement on the derivation -- use of these so-called excess embryos for the derivation of human stem cells.

DR. GREIDER: So that is one form of embryo research.

DR. SHAPIRO: Absolutely.

DR. GREIDER: Okay.

DR. SHAPIRO: And the question is whether we would want to contemplate comment on anything else to other forms and that is the issue I was not deciding in any way but just raising.

Eric?

DR. CASSELL: Well, I think Bernie is absolutely right. I think to go into the broad issue of embryo research would just get us into terrible trouble. On the other hand there is no ducking the issue -- the question that when you talk about spare embryos they may be spare but they are embryos and, therefore, that is why I think their moral status has to be considered.

For example, what is in here about the moral status and the whole thing about oocytes and so forth is cut with a very broad -- or painted with a very broad brush and not at all subtle enough to allow us to get at. Otherwise, we have -- we sound like, oh, well, now there is a use, now murder is okay, and that is always a dangerous policy.

But I do not think that is what the issues

are. I think that the moral status issues are much more complex than that and that they can be made clear enough to a public that wants also to have transplantation results and so forth to come out so that it is true. It is not specious reasoning and it is a good support for moving forward and providing excellent research results and clinical results.

DR. SHAPIRO: Bette?

MS. KRAMER: I do not have a comment. I have a question for Bernie.

And that is, Bernie, in your reading of the political landscape on the basis of your experience in the Human Embryo Research Panel and now confronting this issue, how do you think -- what do you think the response might be in terms of responsiveness of the public to case two? That is the use of spare embryos. Do you --

DR. LO: I would distinguish the reaction of the public and a reaction of some members of Congress. I think the reaction of the public -- I am not sure. I would be willing to say that it would be possible to draft an argument for allowing embryo research in Carol's sense in the very restricted case of derivation of embryonic

stem cells.

I think you could make an argument that a substantial number -- portion of the American public would find acceptable as public policy.

There is a separate question which I defer to Rachel. She is much more expert in this than I. But, you know, for certain members of Congress this is a real gut issue and what happened in 1994 was that they threatened to hold up the appropriations for both NIH and HHS on this issue. They were willing to do it. They had the votes at that point to do it.

Now whether they have the votes this year to bring this issue to that level I am not sure but certainly the sentiment among some members is probably there. I mean, make no mistake about it, there are some people who feel very, very strongly against this issue and, you know, have -- are willing to use a range of techniques to achieve their goals.

DR. SHAPIRO: I think -- I am sure what Bernie says is absolutely correct. I think we -- my own view is we have to be careful about basing our judgments on the realities of certain political factors that are out there.

I mean, I think we should not ignore them. I quite agree we should be cognizant of them and in some way they will impact what we do. I am very sensitive to that.

On the other hand we have to be -- there are all kinds of other people doing that work and we have to be very careful when we tread on those waters because that is -- we have another set of responsibilities --

DR. GREIDER: Without question.

DR. SHAPIRO: -- which we have to pay some attention to. So while I agree with what -- I mean, the sense behind what Bernie has said that we ought to be conscious of this and we ought not to intentionally shoot ourselves in the foot and so on. I want to also be cautious about what we do and what we say and how we motivate ourselves in that area since that is not what we are sort of specifically charged with.

DR. GREIDER: No.

DR. SHAPIRO: But we are specifically charged with having some useful impact and so that brings this in one way or another so I just want us to be cautious in that area.

As I look at the various kinds of moral

status, moral standing issues which Eric has raised and which, of course, is part of the foundation of anything we will say, these things are -- it is proved over many millennia extremely difficult to establish in precise terms the moral standing of any living organism. It does not matter whether we are talking about a very small organism, or a big one, or a huge one, or other kind of animals. It is a very difficult thing.

And what we are saying when we are saying that, well, for stem cell research this is okay. Excess embryos for stem cells, this is okay. What we must have in mind here is that there is some benefit out there which overwhelms the particular other set of concerns, moral considerations we have with respect to whatever we think the moral standing of the embryo is. There are another set of moral issues over here having to do with benefits for future research, relief of suffering, et cetera, et cetera, that overwhelm that.

It seems to me, therefore, very hard to make the argument that this would only be true in the case of stem cells. There is nothing else you could imagine for which this would be true.

As a matter of fact, if I understood Dr. Gearhart -- and, Carol, I really defer to you and others to know much more about this than I know -- what motivated his early work or the work that he did at least as described briefly to us was when things go wrong in the development of young infants they go wrong very early and that is why he was interested in working back in this area as I understood what he told us.

Therefore, it is by no means clear to me that a stem cell is a kind of unique example of what could go wrong or what might -- where interventions very early on in embryonic development might yield enormous benefits. Maybe they will, maybe they will not. I am not the one that is qualified to say but I really believe that we are -- even in case two the argument is not clear to me to just say it is human stem cell and nothing else.

I think we have to have limits but the limit it seems to me just in terms of the moral argument, I am putting the political argument aside for a moment, is that you have a sufficiently compelling project so that it overwhelms or in some sense counterbalances the concerns you have in another direction.

Now I do not have any other project in mind here and I am not the one that should say what those are but it seems to me we should think about that through carefully even if we decide for other reasons we do not want to make that recommendation now or we do not want to deal with it now that we at least indicate, it seems to me, that this is a matter which we should continue to consider.

And if I say that, just to put all the bad news on the table right away -- if I say that I then ask myself, well, what is the difference now between cases one and two -- in a moral sense. I understand the -- or at least I have a vague notion of the politics involved here. What is the distinction between that and cases three and four? Okay. What is it really that is driving me in a moral sense to make these distinctions?

Now case three was put in that position rather than the fourth position as I understood Fletcher because he thought it had enormous promise although he then pulled back and said but it is the one we know the least about. And I think that is true. We know the very least about that and, therefore, it is very, very difficult in my

calculus to start making arguments about this because we know so little at this stage.

Case four on the other hand is something we know not everything about but we know an awful lot about four and what distinguishes it, I guess, is that those embryos -- is intent because that -- those embryos were not made for the purposes of procreation and there were just some so-called excess. These are made specifically for that purpose.

And I tried to think through myself -- just this is initial thinking and I -- please do not hold me to anything I am saying. I was just trying to think this through last night. I just tried to ask myself in a clear way why -- what is holding me back as opposed to the country or the rest of the commission, back in this area. And the thing that really -- I think there is a difference.

I have not been able to articulate it well or I certainly cannot defend it but the thing that I kept coming back to, I kept asking myself would I advise anybody to do four. Would I advise a woman or a man or somebody to do four just if I was giving them personal

advice as opposed to policy issues which we are considering. My answer was, no, I would not advise them to do it and I am going to have to work that through in my head as to why I feel that way and whether this is just my peculiarities and particular anecdotal issues or I really have a moral reasoning for it.

But I think that the purpose for all this rambling is that I do not think it is quite so easy to make a sharp distinction between one and two and three and four. I think for purposes of our response to the President it might be useful to make that distinction for various reasons but I -- as I try to think through the moral issues here it was not so easy to make those distinctions even though I believe there are some there.

So that is a lot of rambling. I apologize. I just want to sort of have us think about these things.

Steve?

MR. HOLTZMAN: It is excellent rambling. It is not rambling at all. Okay. It is spot on. And why I say that is I think through the first issue of do we have to cast the net wider than embryo research for the purposes of making stem cells, I do not think we have to.

Our reasoning in support of it will have implications beyond it, which is the first part of your nonrambling ramble.

All right. And the model for how we can handle that is actually in the cloning report where we have a footnote that says it will not escape observation that our reasons for saying not the following in the case of somatic cell nuclear transplant would also apply to twinning but we are not taking up that question but it does point you very quickly to looking at the basis of your reasoning.

With respect to the second part of your rambling, nonrambling, all right, is what it suggests because what you were doing was this balancing of the value of the embryo versus the good to come out of it and then you find yourself asking, all right, well, the value of the embryo is unchanged it seems whether or not the intent of what was behind the intent of its creation, all right.

And what that suggests at least in the way I conceptualize the problem is that one ought not be situating the locus of the moral question in the embryo.

It is rather in the relationship in which we stand to embryos and the profound point I took Fletcher to be making is where technology is changing, all of a sudden how we run into it and where we run into embryos is rapidly changing.

I think it is a very complex issue but it is a way to start to think about it and I gave Eric some -- because you said, to pick up your rambling, "I would not go to someone and say go donate this for research purposes."

But there are technologies available now to sustain ovaries in culture. All right.

So you imagine a woman who gets an ovariectomy because she has a tumor and now you have got this ovary sitting in a culture dish which can produce eggs. Now you can have research purpose embryos. Are your intuitions the same? Probably not.

DR. SHAPIRO: Probably not from what I was thinking about.

MR. HOLTZMAN: And what does it tell you because all of a sudden now it starts to say that the

locus of the moral concern has to do with how we stand it in relationship to issues like reproduction or issues like raising children.

DR. SHAPIRO: You are quite right. My own intuition was exactly as you suggested and it had to do -- I mean, my initial reaction had to do with the limited amount -- the limited capacity of women, for example, limited number of oocyte that a woman can produce in her lifetime and so on and so forth.

But I know, Eric, I want to come -- well, why don't we go to you --

DR. CASSELL: No, go on.

DR. SHAPIRO: No, go ahead.

DR. CASSELL: Well, what has come up in this and in your intuitions, and I agree with your nonramblings, is that what we talked about yesterday is the embryo as related to. The embryo is not this isolated thing out there which is politically what it has become.

DR. SHAPIRO: Right.

DR. CASSELL: The undefended embryo which, you know, there are some people defending it and other people attacking it, it is not that at all. It is something in

relationship to its donor, its relationship to knowledge. One of the troubles about the category three is if you knew for sure what would happen that would be one case but you do not know for sure. So if that has a bearing on it then knowledge about it has a bearing on it.

Well, if knowledge has a bearing on it and its relationship to how it came to be and to the people around it has a bearing, that is what I mean by moral status and working those things through, coming to understand what is it rather -- and moving off the dime that has held us now for this generation of you are against the embryo or you are for it. There are some embryos I have known but -- so I think that is where -- and that is what your intuitions are.

DR. SHAPIRO: Right.

Let me -- also this discussion reminds me of another aspect of the report which we have not yet discussed directly although we have had some presentations, which I think will be quite important and will, in fact, inform -- certainly would inform how I would feel, may or may not inform how others would feel about it. And that is -- I mean, I think we understand

carefully enough what human embryonic stem cells are, where they come from and so on and so forth.

What I do not think we have talked about enough or received enough focus on is a kind of working vision of how this science is developing, that is whether we are about to be able to figure out how to get embryonic cells without having an embryo for example. It may be near or far away, again I am not the person to say but I already hear scientists talking about it. Whether this is pie in the sky or not someone else will tell me.

But I really do think and I mentioned this to Eric that we really ought to have some very, you know, distinguished scientist working on the frontier on these matters really lay out for us at least their vision of what the -- what it looks like over the edge so to speak in these scientific areas because I think it makes a big difference at least to me whether -- you know, what are the ultimate paths to the -- another way to put it -- to the benefits that we see here. Is this the only one? Is it the only one that we are going to deal with in the next 20 years?

And I think someone like Bridget Hogan, for

example, but other people of that stature who could share that vision with us which we could then, so to speak, triangulate with other scientists who are also working in this area, might really give us a better grounding on how we are dealing with this issue in some sense.

And so we will try to get something like this together between now and next meeting if we can find the right people to do it.

Steve?

MR. HOLTZMAN: A couple of subjects for ramblings for people to think about. One comes out of an interchange that was somewhat abbreviated between Alex and myself. Beyond the question of federal funding it is natural to find yourself asking the question of whether or not there ought to be for profit sale of embryos. All right. So for your ramblings consider that under U.S. law you may not sell organs for-profit. You may not sell blood for profit. You may sell plasma for profit. All right. You may sell your gametes for profit. As we take a position, if we do take a position, how do we articulate the basis of why we are taking that position?

The second is one of the things that was

emerging yesterday -- remember when we talked about case one and case two and case three, and you were pointing to that -- let me put three and four together for the moment for simplicity, that is research-purpose embryos. There are two questions. Federal funding for use of ES cells derived from them and federal funding for their derivation.

If we come out with the position that no federal funding for the derivation for research purpose embryos, that is no research purpose embryos, Alex was saying that forces us to the position of saying no federal funding for the use of ES cells which were originally derived from that source.

If you say that and say there is that connection between the two then you have to ask yourself what do you think and say about connections between use and derivation in the other cases. For example, the classical argument in terms, of is it okay to use the organ or the cells from the fetus in the abortion because you are not complicit and there are two senses of complicity. In a logically complicit and then also in a bad thing. I am just dealing with the first.

Alex's argument is that there is complicity in the logical sense. We have to make sure that if we reject the complicit argument above what sense we are doing -- so just ramble on that.

DR. MESLIN: Steve, can I just ask almost a selfish question because you seem to be so close to suggesting what some of those justifications might be? Would you be prepared to ramble for a minute just using the example of whether there is inconsistency between the purchase or sale of particular human biological materials for lack of a better expression. What is on your mind as you ask us, certainly from the staff's side as we draft some of these things, that would be morally relevant just to flush that out a bit?

I mean, there could be a “so-what” argument. So what, we may just stipulate that plasma is different from it and come up with a not terribly helpful --

MR. HOLTZMAN: No, no, that is okay. No. I mean, it is -- pshew. I think Eric is so right here, is that -- you know -- well, what a thing is, is not distinct from how we regard it and the relationship in which we stand and act to it. That is defining of a thing. I am

going to get very philosophical here. I am sorry. Okay. And that involves political context, historical context, okay, relational context. So I think blood has a certain kind of resonance and rhetorical role in our lives and society and symbology and meaning, if you will, that has led to certain ways of regarding it that plasma does not seem to have. Okay.

I think that the way people -- you know, when people looked at gametes and how that historically arose as a practice and then sort of tacked on afterwards was whether or not people -- they are just gametes, all right. But now when all of a sudden, the gamete, you can quickly turn it into the embryo.

Again I kind of rambled myself in Princeton about this, is that there is a profound -- there is a profound change in our relationship to these things taking place. When you move from embryos being things which exist only in uterus in live women, which again give rise to children, you have one relationship. It is a very, very different relationship where embryos are things that can be created in culture dishes not only from the union of two haploid genotypes but, in fact, from emptying one

out, right, and dropping in a diploid one from my skin cell. We are in the process of changing our relationship to these things and the moral categories reflect those changes in relationships.

This is not easy stuff, guys. All right.

DR. SHAPIRO: I think the issue of -- I cannot remember who it was but one of the -- one of the people who appeared at one of the recent hearings on the Hill -- I do not remember who it was. I know I read a whole bunch of documents that dealt with people appearing before Harkins and Specter and others dealt -- I thought in a not -- well, we try to deal with this issue that is -- these one-to-one relationships between moral categories and biological categories are just not adequate anymore. That is, that it is another way of saying embryos are not equal because there is other characteristics depending on this, that and the other thing, and that is -- and it was an argument of that nature.

MR. HOLTZMAN: But you see the deep argument is actually they never were. We thought that that was the basis but, in fact, it was not the basis. We were misled when we started thinking about these things to think that

was what it was but it was not.

Which, I think, also can go to a framework -- I mean, I have hinted at this before -- is that we seem to in this balancing, want to acknowledge people who have a belief about the metaphysical stem cell who says the embryonic stem that says we want to respect your view but now we are going to override it for good research or therapeutic reasons but dammit if it was a person that would not have been sufficient.

All right. So it is disingenuous and I think one -- you know, Dehanis Kaplan, Elias' response in the embryo report, I think, was right in saying that they may believe that they were not going to make a call but the way they made the call, in fact, chose the status.

There is another way of doing it, which is to say that what we are respectful of and that is consistent with that position of those who view the embryo in a very special way is the role of the embryo in human life, all right, and our relationships -- and how we view reproduction and whatnot, and that is a consistent value that does demand respect. That is the kind of value which you can put in the pans with the therapeutic benefit that

could be derived. All right.

If you are respecting their view that this is a person, a full-blooded person, it trumps because I cannot kill you for a therapeutic benefit to others.

So you cannot respect that but you can respect everything else that is around it. Okay.

DR. SHAPIRO: When you say you cannot respect, what does --

MR. HOLTZMAN: Respect requires that it trumps in this --

DR. SHAPIRO: Oh, you cannot respect it in the sense of respect meaning equivalent to a person?

MR. HOLTZMAN: Yes. You cannot say --

DR. SHAPIRO: Yes, I understand.

MR. HOLTZMAN: Yes, correct.

DR. CASSELL: But we have different categories of persons.

MR. HOLTZMAN: I am not -- I did not want to get into that level of detail. None of which would allow you to kill one of them --

DR. CASSELL: But they would allow you to put another value in place of their preservation. We do that

with people who have terminal illness. We do different things depending on the situation. Now the surplus embryo, it is an embryo to die. That is a different state than the embryo made for and so forth. I mean, those are to be argued out. Those are not for me to do that at this moment although I can tell you this: A commission where you get to have this conversation cannot be all bad.

(Laughter.)

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I would just like to express some of the thoughts that I have had and I have listened very carefully to everyone else and I am probably in a state of being able to be convinced to think otherwise than I am thinking right now but there are four points that I would like to make and the first one is the one that Alex made first yesterday and that is that it seems inconsistent to fund the use but not the derivation of stem cells so in my view why would we not lift the ban on funding of embryo research if we are going to honestly take a look at this issue and what it means for our future and the future of medical research.

The second point, I was struck by reading the

paper by John Fletcher that if one lifted the ban on embryo research that that would give Geron a monopoly on the cells that they have already produced so that perhaps that would be something that would be in their favor more so than in the favor of society generally.

And then the third concern that I had is that we are not sure what is already happening in fertility clinics. Kathi mentioned that what she has found out in talking to people who work in fertility clinics is that they are already creating embryos for research purposes so there may be activities going on that we are debating but people are just forging ahead with them already.

And then the final concern that I have is what is ahead generally. We think most, I guess, about medical advances and Fletcher talks about a moral evolution as if we somehow in the natural course of things would come to accept what seems to us perhaps unacceptable now or at least questionable. But what disturbs me despite thinking about the medical advances is this specter of eugenics and I think our country has had a history of eugenics movements. I think that in our society now we have a lot of separation and segregation of ethnic groups. We have a

lot of ethnic hostilities.

I think that the more we get the power to control genetic outcomes in organisms that that might not always be used for the good and so I am just concerned about what will happen with the opening up of research in this area in that regard and I think that we need to be concerned about those kinds of things even though they may seem fantastic to us at this point. But there are possibilities that may be beyond our imagination right now so those are the concerns that I have.

DR. SHAPIRO: Well, thank you. That is very helpful. I would just make one or two points with respect to some of the issues that you have raised. I am also in the same position of uncertain where my mind is going to end up on these things. It is still in some flux.

But, of course, it is true the issue of how we deal with the public-private universes in this respect in this country is a whole separate -- it is not a separate issue but it is an important issue. We had the case yesterday of I guess people in France worry that they cannot create these but they import them. Well, we could easily be in the same position, only importing from one

sector to another within our own society and that is an issue.

You know, I always liken these things to distinguish between what is morally permissible, legally permissible, and available for federal funding. Those are all different issues. So in our country right now this is all legally permissible. There are no laws against it, period, whatever our moral views are. But they are not -- a lot of these things are available for public funding and we are going to have to -- we are certainly going to have to deal with this.

Regarding the last issue you raised, those are that, in fact, scientific discoveries are in some sense Janus faced, that, is they could be used for good or ill is, of course, absolutely correct. And -- but that is of -- that is even older than the rest of the issues that we are dealing with and a serious problem and never will go away. The applications of science is where they achieve their moral significance. And whether we use something that is morally sort of uplifting for us as opposed to the reverse is a very, very serious problem and so I -- not that I know exactly what to do about it but I certainly

recognize it as a very serious problem.

Well, Eric, you will have the last word.

DR. CASSELL: Yes.

DR. SHAPIRO: Or actually we will go to Eric, then Arturo, then we are going to adjourn.

DR. CASSELL: And that is there is one distinction in this research -- in the research we are talking about there is a distinction between the scientific research to get knowledge and the way the excitement is bred in this which it is not just knowledge, it is life saving, it is therapeutic, and that is a difference, and it has a symbolic difference. The Frankenstein monster is the epitome of the research for just knowledge or knowledge gone awry. I hear that point also. Knowledge going awry. Whereas -- and it is hard to sell pure knowledge in this particular battle, this particular battle, despite that all men by nature desire to know.

But the promise of life saving is the promise of transplantation and the promise of better gene therapy and so forth, that is different, and that has a different standing than just the search for pure knowledge.

DR. SHAPIRO: Arturo?

DR. BRITO: I have not say anything because I have been really thinking through this and I did not want to say anything that was going to open up a can of worms like I did yesterday but I want to restate that in Princeton I stated that I have a lot of reservations. I understand that this is where we are supposed to set public policy and we try to be as objective as possible, et cetera, but I do not think what I am reflecting as a minority on this commission is necessarily the minority with people that are not on this commission.

And I have a lot of reservation about the use of fetal tissue from elective abortion for this purpose and the reason I am bringing this up now is because in hearing Eric and Steve's comments I am hearing something that sounds to me right now -- I have to think through this to see if I am right -- but it sounds to me very hypocritical because we keep going back to the focus of intent and taking -- and understanding the relationship of the embryo to its environment. That is where it is important.

You just cannot take this cell -- okay. Yet -

- well -- and cells that come from aborted fetuses, from electively aborted fetuses, that is an environment they are coming from so it would go to the complicity issue. It just sounds very hypocritical to me.

And what the intent of that embryo was to become a child. So, therefore, I just do not think -- if we are going to use those arguments we have got to be very careful if we are going to use them across the board or just when -- once again it sounds to me -- it just sounds very hypocritical.

MR. HOLTZMAN: No, actually I agree with everything you are saying. One point I was making about it to Harold is we need to understand if we are going to say it is okay from those cases, all right, we need to be articulating a framework that explains why it is connected or why it is not and then be consistent.

DR. BRITO: Right. Okay. Absolutely.

DR. SHAPIRO: Nothing in this area is slam dunk.

DR. BRITO: No, it is not.

DR. SHAPIRO: These are all tough issues.

Trish?

DR. CASSELL: Princeton did not do so well yesterday, did they?

DR. BACKLAR: One thing --

DR. CASSELL: Princeton did not do so well.

DR. BACKLAR: I just want to say one thing for Arturo. There is a difference between intent and potential. The embryo does not have intent, it has potential. It is the people who are involved with that material -- I want to say material because it may or may not become an embryo that has some intent and the intent may be to have a child or the intent may be to do research to make benefits for others. So we need to differentiate between those two concepts.

DR. BRITO: I think I do differentiate but I will put it in writing and I will express it.

DR. CASSELL: Otherwise the HIV virus has intent also.

(Simultaneous discussion.)

MR. HOLTZMAN: A good example is elective abortion in the case of rape or incest cases.

DR. BRITO: Well, then we get back to the basic issue but I do not want to just -- what I am saying

is that it sounds very hypocritical to me. Maybe when we see it in writing then it will come out but it just did not sound very consistent.

DR. SHAPIRO: Trish just reminded me that --

DR. BACKLAR: Lori Andrews.

DR. SHAPIRO: -- Lori Andrews' article is in the packet and Trish believes some of us would benefit by reading it carefully and so I pass that suggestion on to you.

DR. BACKLAR: But the public-private issue she addresses very, very well.

DR. SHAPIRO: Thank you.

(Whereupon, the proceedings were adjourned at 2:28 p.m.)

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