33RD MEETING

OF THE

NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

OPENING REMARKS

DR. SHAPIRO: If I could just make a few comments. As I indicated yesterday, we are going to shift our agenda around today and try to complete our work for this meeting on the stem cell issues and then turn to the international issues as opposed to going at it the other way.

So we will proceed immediately to return to our stem cell discussion.

I do want to make one other just brief report. It is not even a report. Just a statement to the committee. We expect to be delivering the Human Biologicals Material Report to OSDP and the President later this week so it is just being in the process of production and we will get copies to every member of the commission and so on if people want extra copies. At least within a few weeks those will be available but there will be some small number available to us right away. But that is really done, it is just in the process of production and will go later this week.

THE ETHICAL USE OF HUMAN STEM CELLS IN RESEARCH

DISCUSSION CONTINUES ON DRAFT REPORT

DR. SHAPIRO: Returning to the stem cell issues. A small number of us got together late last

night, myself, Eric Cassell, Eric Meslin, Alex, and Jim at least for part of the time, to try to just put together -- take all the recommendations we -- all the suggestions we got yesterday regarding changes in the recommendations and tried to put them, as you can see, on four or five sheets of paper and my intention today is to go through these, adopt and change as necessary as the commission wants, and then assume that is going to be the set around which we will build the text and so on. There will be further refinements and so on which we will communicate as we usually do as we go through this with the intent of getting this report out pretty quickly.

So that is the intent. Obviously we thought we were running out of steam late yesterday afternoon, we did not have all that much more steam late last night but I think I did at least scan these early this morning as we went to reproduce them and it seemed to me at least on the whole to get the gist of what we had suggested.

So perhaps what I intend to do this morning is just to go through these one by one and if there are serious differences, if we have misstated or misinterpreted what it is that the commission as a whole was thinking, we ought to resolve that right now. I do

not think we ought to worry about small wording differences although we would be grateful for those suggestions as well obviously because we are going to have to refine and review this language as we go forward to say nothing of the changes in the text that will be coming along.

So if there is no objection we will just go through these one by one. Has everyone got one of these in front of them so we can have this discussion? Okay. Let's go, therefore -- we now have, if you look at this sheet, we now have 14 recommendations, including one, the last one, which we did not even discuss yesterday because we just never got to it. That was (N) I believe. And so -- but the others, I believe, we discussed. So let's just go through them one by one. I will read each one as you think it through and then we will see what changes and so on you might wish to suggest.

Recommendation one: "Research involving the derivation and use of embryonic germ cells from cadaveric fetal tissue should continue to be eligible for federal funding. In addition, existing statutory and regulatory provisions should be amended to include the derivation and use of EG cells for research

purposes." That is close enough to what we decided. Okay.

Recommendation two: "An exception should be made to the present statutory ban on federal funding of embryo research to permit federal agencies to fund research involving the derivation and use of ES cells from embryos remaining after fertility treatments under appropriate regulations that include public oversight and review." The substance of that has not changed but the language has changed.

Steve?

DR. HOLTZMAN: This is a substantive point and then just a little stylistic point.

DR. SHAPIRO: Get a little closer.

DR. HOLTZMAN: A substantive point and a stylistic point. I believe, as written, this unintentionally endorses the view that an exception to the current ban is necessary.

DR. SHAPIRO: For use.

DR. HOLTZMAN: For use.

DR. SHAPIRO: A good point.

DR. HOLTZMAN: And, therefore, and this comes a little bit from the discussion with Carol, this is stylistic, why not conform more to what is the style of the previous recommendation such that you would start

with research involving the derivation and use of ES cells from embryos remaining after infertility treatments should be eligible for federal funding under appropriate, and then explicate in the text that follows about there may be a need -- there will be a need for a change in the legislation.

DR. SHAPIRO: How do people feel about that?

MR. CAPRON: An alternative -- well, I just -- what I was going to suggest is that we only address derivation here and then in the commentary say it has already been -- but I --

DR. SHAPIRO: Okay. I mean, I think that is a very good point. We just -- as you pointed out, we just did not think it -- think it that clearly last night. But I think we are all agreed on the substance of this so that I do not think there is any need to have discussion.

But, Steve, do you want to draft at the break or now or whenever, just draft the change and we will take a look at it because I want to -- we will reproduce a set of these before we leave today so people can take it with them in case they want to sort of call back again but thank you very much. That is a very useful point.

David?

DR. COX: There is two components to this. I really like what Steve said because it confounds -- I mean, we do not want to confound the use.

DR. SHAPIRO: Okay.

DR. COX: On the other hand, the wording -- an exception should be made to the present statutory thing is very good because it shows that we are not revising the law but we are making an exception to it in terms of embryos. So it is almost two separate points and I really like the exception part but to move out and sort of say -- when you are doing this to make it clear that, you know, it should be okay to continue using it because that is okay right now but the new thing -- it is almost like two is two different concepts put together.

DR. SHAPIRO: I think there is a couple of choices here. We could do two different recommendations, for example, or put some in a commentary and some --

DR. COX: Right. Those are details.

DR. SHAPIRO: Yes.

DR. COX: I mean -- because I am completely in favor of those two points. I would not want to see the wording -- that initial wording change because it really, I think, is very respectful.

DR. SHAPIRO: Okay. We will work on that but I think we all understand what we want to achieve here.

Okay. Let me do -- recommendations three and four are so similar but we -- as we decided yesterday -- we would separate them because we want a commentary following each one of these to be somewhat different so I will read them both together and then there will be comments on -- you may want to think about it.

Recommendation three: "Federal agencies should not fund research that makes embryos through in vitro fertilization solely to generate human ES cells or that uses ES cells so derived."

Recommendation four -- we will come back in just a second. "Federal agencies should not fund research that uses somatic cell nuclear transfer with oocytes and generate human ES cells or that uses ES cells so derived."

Carol, and then Steve?

DR. GREIDER: This is just a wording point but the way that it currently reads, recommendation three, "Solely to generate human ES cells." I do not know that we are necessarily saying that one should not do that solely for ES cells. We are saying that you

should not create research embryos. Is that -- what if you create a research embryo to --

MR. CAPRON: You cannot do that now anyway.

DR. GREIDER: I see.

DR. SHAPIRO: Steve?

DR. HOLTZMAN: It is a striking fact that we have "solely" in recommendation three and not in recommendation four, and that could either be stylistic or --

DR. SHAPIRO: I think it was --

DR. HOLTZMAN: -- late night.

(Simultaneous discussion.)

DR. HOLTZMAN: But there is a substantial point for us to think about for a moment about --

DR. SHAPIRO: Sure, absolutely. Which is?

DR. HOLTZMAN: Which is are we going to simply address no research purpose embryos -- no federal funding for research purpose embryos for stem cells. So are we going to say the broader --

DR. DUMAS: That is right.

DR. HOLTZMAN: -- when something is used for stem cells and something else. Now I think it raises the question that you have "solely" in one and not the other. All right.

DR. SHAPIRO: Our intention, if I recall, last night was we had -- were not making a distinction that I recall. Now I came in after --

MR. CAPRON: This language -- one of the things that was passed out previously had this language. As I understood, the "solely" there is differentiated from making embryos for fertility purposes and so it is -- and if we said through IVF to generate ES cells then we would appear to encompass excess embryos as well. That is to say the embryos remaining after fertility, someone would say, "Well, you are in effect involved in --"

DR. SHAPIRO: We need some adjustments. It is okay.

MR. CAPRON: No, I mean, perhaps we ought to change the wording but the intention was not to allow any implication that what we were talking about could be read back to encompass --

DR. DUMAS: I think the term "solely" is needed in each case there. As I understand it, what we are saying is that when the only objective is to generate ES -- so I am speaking to keep the term "solely" in.

DR. SHAPIRO: Steve, do you have any concern with using "solely" in both these cases or a reason why we should not?

DR. HOLTZMAN: I mean, read "solely" the way Alex intended it, I think, is a good point. All right. I am just -- as I look at it more closely, the research we are talking about is research to make an embryo as not eligible for funding the way we have read it. I think what we really mean is research to generate ES cells wherein the -- it is from an embryo, which was a research purpose embryo. So I would take a crack at rewriting it. I think we need to just flip it around.

DR. SHAPIRO: Right.

MR. CAPRON: We said federal agencies should not fund research to generate ES cells from embryos made solely for that purpose.

DR. SHAPIRO: Right.

DR. DUMAS: And then we need to have it that way because as I understand it we are recommending support to generate -- I mean, to -- yes, to generate ES cells from embryos that have been discarded.

DR. SHAPIRO: You have to remember that we want to write this so that it not only deals with the creation of ES -- one or the other of these techniques but also the cells that they derive from them.

DR. DUMAS: That they derive.

DR. SHAPIRO: We need language that gets both of these things in.

MR. CAPRON: Can we call them IVF embryos? Do we have to say through IVF?

DR. SHAPIRO: I do not know what language is --

MR. CAPRON: In ordinary language now -- if we were saying federal agencies should not fund research to generate human ES cells from IVF embryos made solely for that purpose, solely for research purposes.

DR. SHAPIRO: We need another sentence which talks about the uses of ES cells.

DR. DUMAS: I think this one is clear. I think this is clear, Alex, and you remember the -- a lot of different people are going to be reading this report and to just refer to IVF might not be clear enough. I like it like it is.

DR. HOLTZMAN: The problem with the way it is, Rhetaugh, is the federal funding is referencing the making of the embryo as opposed to the federal funding for the activity of generating the ES cell. That is what we are trying to address.

DR. DUMAS: Well, but -- go ahead.

DR. SHAPIRO: David?

DR. COX: I would the wording the way it is. In order to make the ES cell you have got to make the embryo and so this is in the order that is done.

DR. HOLTZMAN: But the federal funding will likely be of the generation of the ES cell and we are saying do not go get a research purpose embryo from an IVF clinic.

DR. DUMAS: That is right.

DR. HOLTZMAN: And the federal funding may have had nothing to do with that research purpose embryo's generation in the IVF clinic.

MR. CAPRON: And in recommendation four we actually talk about uses somatic cell nuclear transfer with oocytes to generate and there it is really speaking only of the technique. I mean --

DR. COX: Okay. I get it.

DR. HOLTZMAN: I think what we want is something like this: "Federal agencies should not fund research to generate human ES cells made from IVF embryos made solely for research purposes, nor fund research using such ES cells."

DR. DUMAS: That is not as clear --

MR. CAPRON: You do not need the first --

(Simultaneous discussion.)

DR. CASSELL: Sleep muddles the mind, Harold.

MR. CAPRON: -- to generate X from Y.

DR. SHAPIRO: Sleep was supposed to help you. That was your claim last night.

(Laughter.)

DR. _____: Eric, do that hypnosis thing on yourself again.

(Simultaneous discussion.)

DR. SHAPIRO: I want you to describe that technique to the whole commission at some stage.

Kathi?

DR. HANNA: I am just going to try and read what I put together from what you have said. "Federal agencies should not fund research to generate or use ES cells from embryos made via IVF solely for that purpose."

DR. DUMAS: But, see, that is not clear. That sounds like you are saying "solely for IVF purposes."

MR. CAPRON: Solely for research purposes.

DR. DUMAS: I think it is clearer the way it is.

DR. HOLTZMAN: It is clear the way it is but it is wrong. It is that simple enough.

DR. DUMAS: I do not understand why it is wrong, Steve, so it is not simple to me.

DR. HOLTZMAN: It is not wrong the way it is. The question is whether --

DR. DUMAS: It is not simple to me.

DR. HOLTZMAN: Yes.

DR. BRITO: I think -- I guess we are not raising our hands here but I guess that the -- I disagree. I think I agree with what Steve just said because solely to generate human ES cells implies that you create an embryo for research purposes as long as it is not for -- and I know our mandate is to worry about ES cells but I worry about a loophole here somehow that somebody could create an embryo for other research purposes and then as a secondary be able to use it.

So I think that "solely" has to define for research purposes.

DR. SHAPIRO: Okay. Kathi, do you want to read your's because it sounded right to me from what you said?

DR. HANNA: "Federal agencies should not fund research to generate or use ES cells from embryos made via IVF solely for research purposes."

DR. HOLTZMAN: Right.

DR. SHAPIRO: That is correct.

MR. CAPRON: We need the word "human" before ES.

(Simultaneous discussion.)

MR. CAPRON: And then recommendation four should parallel exactly.

DR. SHAPIRO: Yes. And the -- and are we agreed that we -- that was the intent although we did not quite do it. The intent was that three and four should be parallel to the commentary that follows them. It is not the same so they will not be right beside each other then. We will have separate commentary.

Carol?

DR. GREIDER: This is just a minor point about four. The SCNT with oocytes I think should read SCNT into oocytes.

DR. SHAPIRO: All right. Is there any further comments on those two?

Let's now go to recommendation five. I am sorry Diane is not here because this is, in part, modeled on the work that she did yesterday but let me read it to you. This has to do with -- if I could use the expression "consent/donation" language. And it goes as follows:

"Prospective donors of embryos remaining after infertility treatments should receive timely,

relevant and appropriate information to make an informed and voluntary choice. Prior to considering the potential research use of embryos the prospective donors should have been presented with the options of storing the remaining embryos, donating them to another couple or discarding them. If the prospective donor chooses to discard the options of donating to research may be presented during which presentation the person seeking donation should..." and this is the conditions that are listed after that. "...disclose that the stem cell research is not intended to benefit the donor; make clear that consenting or refusing will not affect the quality of any future care provided to the prospective donor; describe the general research area and the specific research protocol if known; disclose the source of funding and expected commercial benefits of the research; make clear that embryos used in the research will not be transferred to any woman's uterus; and make clear that the research will involve the destruction of the embryos."

Now the commentary after that will refer people thinking about this to the points to consider and so on document in the appendix, which contains even more issues that surround it but it seemed to us these were

the basic concerns which we so to speak could not do without.

As you can tell from the -- those of you who remember yesterday, we changed -- these are not bullet forms or a bunch of X's here, but we changed the first X in response to a suggestion from Jim as well as the second X to make sure that we had that a little more accurate. I think it is fair to say that -- I think, Jim, in fact, you were with us when we got to this recommendation and at least that seemed to us to reflect the balance of what we discussed yesterday.

Comments and questions?

DR. BACKLAR: At breakfast this morning, I forget which one of you made a comment about perhaps it should be patient donor. I do not remember who made that comment and I wondered if we want to think about that for a minute.

DR. SHAPIRO: The comment we made -- that was in the next -- it was patient subject which comes in the next --

DR. BACKLAR: But I am also thinking of future care provided to the prospective donor. I am also thinking of some aspect of patient care, too.

DR. SHAPIRO: Yes, that is true.

DR. BACKLAR: I mean, it --

(Simultaneous discussion.)

DR. BACKLAR: -- muddle it up.

DR. SHAPIRO: I mean, I think you are right but I think we should keep the focus on donor here.

DR. BACKLAR: Okay.

DR. SHAPIRO: It makes it clear to me.

Eric?

DR. CASSELL: One of the options is present with the option of storing the remaining embryos, donating them to another couple -- could we change "couple" to woman?

(Simultaneous discussion.)

DR. SHAPIRO: Is that the preference? Does anyone object to that? Thank you.

Yes, Laurie?

DR. FLYNN: On the first X, we had a little discussion about this yesterday, we have --

DR. HOLTZMAN: Louder, Laurie, sorry.

DR. FLYNN: On the first bullet we have "disclose that the stem cell research is not intended to benefit the donor." I wonder if, in fact, we would be clearer if we just said "will not benefit the donor."

DR. SHAPIRO: The discussion -- the reason the intended is there is because, as I recall the discussion and if I have summarized it incorrectly

please correct me on this, was that the donor might receive a benefit. It might make them feel like they have done something important for someone but that is a side benefit. It was not the intention. The intention of the stem cell research was to find something out. But -- and the donor might get some indirect benefit or might feel good about it. It was an attempt to get to that issue that the intended was put in.

DR. FLYNN: Might we -- my concern is that the donor might still be under the potential belief that their own particular infertility case or their own particular difficulties might in some way be enhanced, might be ameliorated by the donation to research. Can we say that it is not intended to provide medical benefit? Something that indicates -- you know, the psychic benefit is there for all research donors. Those things are important but the benefit that people are thinking about when they make these kinds of donations I think is in their own case for their own circumstance.

DR. SHAPIRO: I have no objection to that but, Jim, you were --

DR. CHILDRESS: We were -- as a matter of fact --

DR. SHAPIRO: We talked about doing that --

(Simultaneous discussion.)

DR. CHILDRESS: -- would be one way to state it, sure.

DR. BRITO: What about to disclose that the purpose of the stem cell research is not to benefit the donor?

DR. SHAPIRO: That was --

(Simultaneous discussion.)

DR. BRITO: No, not really. I mean, that way you get across the --

DR. SHAPIRO: I mean, I have no objection to putting that in. What did you suggest, Arturo?

DR. BRITO: Disclose that the purpose of the stem cell research is not to benefit the donor or is not the purpose of using -- that way -- because not intended -- I understand what Laurie is saying. I also understand --

DR. SHAPIRO: I would be just as happy to leave the structure the way it is but put medical benefit, to medically benefit. Would that be --

DR. FLYNN: Yes.

DR. SHAPIRO: -- all right with you.

DR. FLYNN: That would help.

DR. DUMAS: To provide medical benefit.

DR. FLYNN: Provide medical benefit. It just makes it clear.

DR. HOLTZMAN: May I make a brief suggestion that you consider when you are wordsmithing that we have -- it is very pithy right now, like the first sentence to make an informed and voluntary choice but we do not say what the choice is with respect to of the disposition of the embryos is what it is, for example, and then the prospective donor chooses to discard. Now I think we all know what that means but you need to make a decision in the final crafting whether you want to put in what it is those verbs are modifying or what the choice is. Okay.

DR. SHAPIRO: Okay. Any comments?

Let's go on then to recommendation six. As follows: "In federally funded research involving embryos remaining after infertility treatment the donor may not restrict the patient/subjects who will receive the cells derived from the embryos."

MR. CAPRON: It is actually patient-subjects.

DR. SHAPIRO: Rather than slash, right.

Remember yesterday we were dealing with recipient specific, we did not know who the recipient was and so on and so forth, whether recipients were institutions, individuals, et cetera, et cetera. So -- and obviously the commentary will, if anyone wants to

know what patient-subjects are, it will be in the commentary, yes.

DR. GREIDER: Why restrict rather than designate? Restrict sounds to me more like you cannot say that, you know, Joe Blow will have --

DR. SHAPIRO: It parallels the Fetal Tissue Statute. That was the reason. We discussed this specifically but there was no other good reason.

DR. GREIDER: That is a good reason.

DR. SHAPIRO: Yes, Bette?

DR. KRAMER: That could be read or interpreted to say that the donor could specify who it went to.

DR. HOLTZMAN: It could say designate or restrict.

DR. COX: The nice thing about this language to me is that the -- it gets at it both ways in terms of not restricting it because if you -- for us to say that it cannot go to that person or go to a specific person but it can go to anyone else in the world, okay, is not fair either. So that this gets you coming and going. This language is just right, I believe.

DR. SHAPIRO: Again, this is very much parallel to what was in the other area because -- and we are trying to just go the last mile to make sure that

the incentives are not there to behave in what some people think are inappropriate ways.

MR. CAPRON: To confirm what Bette said, under the existing Fetal Tissue Statute it is possible --

DR. KRAMER: To designate.

MR. CAPRON: -- to designate but what it says is that no promise can be made that the donation will be or is made pursuant to a promise to the donating individual that the donated tissue will be transplanted into a recipient specified by such individual. So that -- I mean, it does not rule it out. It just says --

DR. GREIDER: Doesn't it happen in some cases that people do designate?

MR. CAPRON: For fetal --

DR. GREIDER: Under certain cases.

MR. CAPRON: -- tissue?

DR. GREIDER: No, for donor.

MR. CAPRON: Oh. There is no restriction in the Uniform Anatomical Gift Act. You may make a gift to a specific recipient, to a hospital, to a doctor, to a program. You can do any of that. The restriction is under the Fetal Tissue Transplantation Act of '93.

DR. GREIDER: I see.

MR. CAPRON: And we all were colloquially saying it does not allow the donor designation and actually Jim was the one who pointed back to chapter three where I describe it and this language is taken from there and that language reflects the statutory provision I just read to you.

DR. SHAPIRO: Bette?

DR. KRAMER: I am curious. What is the practice in IVF clinics if they want to -- a couple wants to donate the embryo to a specific woman? They are allowed to do that.

DR. SHAPIRO: No problem. We are talking solely about -- we are past that stage when you --

DR. KRAMER: I realize that. I was curious about that.

DR. SHAPIRO: That is allowed. That is, indeed, encourage in many ways. Okay.

If we can, I would like to go on to recommendation seven. Donors, this is the one that used to start with "sale," and that has been rewritten saying that "donors may not profit from the transfer of cadaveric fetal tissue or embryos remaining after infertility treatments." That wording was to taken, you know, to say that reasonable costs and so on can be

reimbursed if people who have -- but there should be no profit involved here.

Steve, and then --

DR. HOLTZMAN: Two questions is the use of "may" as opposed to "should." Just you should noodle (sic) on that. Okay. All right. And then the second is by putting in "remaining after infertility treatment" we have delimited the scope of those embryos which we believe ought not be sold. Right? I am sorry, those tissues or embryos that ought not be sold. I am sorry. Let me back up. That is just about embryos. Do we mean that? I know we do not think that research purpose embryos ought to be sold either. I am asking do we want to delete remaining after infertility treatments?

DR. CASSELL: They permit research embryos so --

DR. HOLTZMAN: They do not permit federal funding. This is not about federal funding.

DR. SHAPIRO: This is not federal funding. This particular one. This particular -- we discussed this yesterday, those of you can remember, and this was a statement someone said yesterday was what we believed about social practice as opposed to what we believe about the federal budget and so on.

Jim?

DR. CHILDRESS: Steve raised an important point. We did, in working over the category of fetal tissue, get rid of following induced abortions -- fetal tissue, whatever the source, and probably we would like to have something broader here as well.

DR. SHAPIRO: Alex?

MR. CAPRON: I asked yesterday whether your language of sale meant to incorporate the costs and you said no, which is why I suggested that we use this language.

DR. SHAPIRO: Right.

MR. CAPRON: On further reflection I believe that we do not want to adopt this language vis-a-vis the donors to explain vis-a-vis programs the view has been if someone supplies cadaveric fetal tissue and there is a cost of transporting it, of storing it and so forth, they should be able to get recompense for that.

Under the Anatomical Gift Act donors are the only people who cannot get paid and that has been a source of contention. You know, would we get -- you know, that is a whole different issue. Will we get more if people could be paid? But I think we open a real can of worms here and get ourselves into the very practice we are most concerned about, which is indirect support of the creation of embryos for research, putting aside

the cadaveric fetal stuff, which is covered by present statutes anyway. Can you imagine a situation in which creative cost accountants brought out from Hollywood movie studios --

DR. SHAPIRO: Or some other industry.

MR. CAPRON: -- or some other industry but I just happen to know that is one of the most creative. Say to a couple, "Well, if you donate we will be able to pay you, of course," and then they have incorporated huge amounts of costs, and the word gets around, as Bette said, before, you know, people go into their fertility treatments knowing that at the end they can recoup.

Maybe they would be -- not only be hoping to have and they would always want to stop their treatment at a point where they could recoup some or all their costs of the treatment and they would be and I -- so -- and I am back on the sense that the couple or the woman donating should not be able to get the costs, period.

DR. _____: Isn't that what this says?

MR. CAPRON: No, it says not profit. It is not for profit which means if she --

DR. SHAPIRO: What Alex is saying is if we want to use the structure, I believe what he is saying is donors may not sell.

MR. CAPRON: Yes. Your original view of it was closer to what we really wanted. The sale should be prohibited and Steve got us into this thing yesterday by suggesting we go as far as gametes. We are going to be dealing with all sorts of situations in which the couple has paid a lot of money and it becomes very attractive to say, "Well, let's stop now. We have still got five. You know, can't we sell five? Couldn't we get a good price for five? If we use these up and then we have got one it is hardly worth it but, you know."

DR. SHAPIRO: How dose the committee feel?

DR. DUMAS: I agree with that. I think that distinction needs to be made between getting money and getting profit. The other thing is that this recommendation, the wording is somewhat inconsistent with the others, and I would suggest that we word it similarly to the others about federally funded research.

DR. SHAPIRO: That is -- I understand the point, Rhetaugh, but we talked about this yesterday. We decided that this was not restricted to federally funded. That is donors may not, if we use sell or may not profit, whichever one we choose, regardless of who they are, where they are or whether federal funds were involved or not. That is what this -- I am not trying

to defend it for the moment. I am just trying to describe what we had decided yesterday.

DR. DUMAS: Well, there is nothing here that makes that distinction. It seems strange that it just shifts from federally funded research. So it might be useful orientation to use a preliminary statement somewhat like the one in eight to ensure that all research involving so and so is conducted in conformance with ethical principles. We recommend that.

DR. SHAPIRO: Well, we certainly have something -- if not there at least in the commentary that precedes it because this is all going to have text separating these things but let's go to Carol and Steve and then Alex.

Carol, Alex, Steve.

DR. GREIDER: I understand the point about sale versus profit but I still want to raise a question about whether we want to say embryos remaining after infertility treatments or we just want to stop at embryos.

DR. SHAPIRO: It is something we are going to have to decide. Let's just see what the other issues are we have to decide.

MR. CAPRON: Well, during our early discussions we said we were not going to allow any

payment to the fertility centers for these embryos either so that they -- because their incentive was to produce research embryos is the most uncontrollable because it is behind professional discretion and judgment, and I -- I mean, I am feeling as though this is a large hole that we ought to spend a few minutes plugging.

DR. BACKLAR: The problem, of course --

DR. SHAPIRO: Steve, and then Trish.

DR. BACKLAR: I am sorry.

DR. HOLTZMAN: I have got a suggestion I feel Alex is probably going to hate. All right. And there is a lot of --

DR. SHAPIRO: Maybe someone else will love it.

DR. HOLTZMAN: Maybe someone else will love it.

I do not know if what I have to say is worth all this trouble either.

I would like this recommendation to be a statement of principle and then let the text get into all the differences between profits and allowable costs, et cetera. So if I were alone in the world writing this I might write it as something like cadaveric -- how do you say that word?

DR. SHAPIRO: Cadaveric.

DR. HOLTZMAN: -- cadaveric fetal tissue and embryos should not be commoditized as objects of commerce and should not be bought and sold, and let everything else go into the explanatory text.

DR. GREIDER: Should not be bought and sold.

MR. CAPRON: How about should not be bought and sold.

DR. GREIDER: Should not be bought and sold.

DR. HOLTZMAN: Just that, should not be bought and sold. Whatever. Just to the point.

DR. SHAPIRO: Say that again just to make sure I get it in my head.

DR. CASSELL: Fetal tissue or embryos should not be bought and sold.

DR. HOLTZMAN: And embryos should not be bought and sold.

DR. SHAPIRO: Trish?

DR. BACKLAR: I think that is good. I think the one aspect here that we have not thought about and that it is the -- the donors who, in fact, are funding the development of the embryos. I mean, they are paying for this.

DR. GREIDER: They are paying for their treatment.

DR. BACKLAR: And paying a lot. And often in these IVF clinics they are really funding the research. And it seems to me that there is something there that I would like to sort of pry apart or think about. I do not know. I do not -- oh, I am sorry. Go ahead.

DR. SHAPIRO: That is not -- I mean, that is true but it is not unique to this kind of clinic or this kind of research, which is funded not out of thin air but out of customers one way or another. So I think that is true. I agree with what you said but I think -- I do not know that we can build that -- you know, I do not know what to do with the information because they have paid for that for some other purpose and we are trying to make sure they are not being induced to do things for yet a further purpose.

DR. BACKLAR: I wonder if one wants to at least make some mention of it. No, you think it will open a can of worms.

DR. SHAPIRO: Jim?

DR. CHILDRESS: That is the sort of thing that can be developed in the commentary in the text and I would just like to say I think Steve's proposal is a good one and this is one area where I think that the commentary will be very important.

DR. SHAPIRO: Now let's go to the person that is going to hate this recommendation. I understand the recommendation -- Steve, why don't you say it?

DR. HOLTZMAN: Carol wants to.

DR. SHAPIRO: Carol?

DR. GREIDER: I just wanted to respond to Trish's comment because I do not think one should necessarily have any commentary to that effect in the text because I think we are trying to separate the whole issue of why they went in for their IVF treatment. They went in for their IVF treatment in order to get pregnant and that was their costs and now we are talking about these things that are remaining embryos and that I think is no longer an issue. So I would feel uncomfortable by commingling those ideas.

DR. BACKLAR: It is not that -- I know -- I am wondering if it should be mentioned somewhere. We are presuming everybody understands that and that we have made the separation and that they have gone in for this reason. I am just -- I do not know whether it should be addressed and if somebody else is going to make a big fuss about it.

DR. SHAPIRO: Alex?

MR. CAPRON: I think there is no harm in explaining our reasoning process. We could take note of

the fact that in the context of the tissue donation, professional services of obtaining the tissue and transferring it are compensable. We have chosen very explicitly to not make them compensable vis-a-vis this process to the people, who as Trish says, have paid for them. And I think, Harold, actually it is somewhat unusual for the extent of their research to have been patient funded. I mean, if you compare it to cancer research, a lot of that --

DR. SHAPIRO: That is right.

MR. CAPRON: And so there will be some people, who looking at that, will say, "But certainly they meant that it is not an object of commerce if I just get my cost back." And you say, "No, no, we do not want --" and we would be very explicit that the risk is that that will give both the program and the individuals the incentive to create embryos for research purposes under the guise for creating them for fertility purposes and, in fact, do so precisely to become an object of commerce to use the --

DR. BACKLAR: That is exactly what I -- I did not want it swept under the rug and I think it is important to explain our reasoning whenever we can.

DR. SHAPIRO: Thank you. Is there any -- is there general agreement then that we will have

recommendation seven and then we will have the words but we are just going to say these are not to be bought and sold.

I do not know if you have the words, Kathi.

DR. HANNA: I just was not clear if you wanted to say should not be bought and sold for research purposes or if you wanted --

DR. HOLTZMAN: Should not be bought and sold --

(Simultaneous discussion.)

DR. DUMAS: Period.

DR. SHAPIRO: What does it say now?

DR. HOLTZMAN: "Cadaveric fetal tissue and embryos should not be bought or sold."

DR. CASSELL: Not "should not" "may not." "Should not" is a mild statement. "May not" would be a matter of law. You cannot sell them. That is all. You cannot buy them and you cannot sell them.

DR. DUMAS: Whoever writes this --

DR. SHAPIRO: We are going to produce a new set of these to go over shortly so why not -- whatever you have there and we will go over it and if there is other changes to be made we will make them.

Let's go on. Now to recommendation eight. We now come to -- the numbers change somewhat now as we

go through the next ones because we have reordered some of the recommendations and the next couple of recommendations deal with the oversight and review process that -- procedure that we want to put in place here.

Recommendation eight begins as -- it goes as follows: "To ensure that all federally funded research involving the derivation and use of human ES and EG cells is conducted in conformance with the ethical principles and recommendations provided in this report. The Department of Health and Human Services should establish a national oversight panel and should have a broad multidisciplinary membership, including members of the public. The responsibilities of the panel shall include..." and here we have a number of bullets and these are what the responsibilities should include.

The first bullet: "Reviewing protocols and approving those that meet the requirements described in this report."

The second bullet: "Maintaining a public registry regarding ES and EG cells..." it says see recommendation nine. That is adequately described below.

Third: "Establishing requirements for and providing guidance to sponsoring agencies on the social

and ethical issues that should be considered in the review of protocols."

Fourth: "Providing an annual report to the DHHS Secretary which would include an assessment of the current state of the science for both derivation and use of ES and EG cells; a review of recent developments in the broad category of human stem cell research; a summary of any emerging ethical and social concerns associated with this research; and a review of the adequacy and currency of the recommendations addressed in this report."

I am going to go to the next one right away and then we will come back and discuss both of these because these were all in one recommendation when we looked at it yesterday.

And the second one, now recommendation number nine, deals essentially with the registry. "The national oversight --"

(Simultaneous discussion.)

DR. SHAPIRO: It is the oversight and review, not the oversight and oversight. "The National Oversight and Review Panel shall establish a public registry, the functions of which shall include..." this is now the functions of the registry. "...maintaining a record of all protocols approved by the panel." The

second bullet: "Maintain a list of certified cell lines derived from these approved protocols."

"In addition, the panel should request from sponsoring federal agencies descriptions of all protocols that use or derive ES or EG cells with any available information concerning research outcomes, including published papers. The private sector is encouraged to submit similar nonproprietary data. This database, which should be linked to the public registry, will be used by the panel to track for the purposes of public policy the history and ultimate use of certified cell lines."

That, at least it appeared to us, made it more explicit and more coherent the description of this oversight and review panel and so on.

David?

DR. COX: So I like it in general but I think, though, when I read the first bullet, okay, I was confused because that bullet, okay, protocols is generic and it involves protocols for deriving and protocols for using. So I would just say there that there is reviewing protocols deriving the cells and approving those, and make clear when we are talk about deriving that the use of protocols is sort of weird because it is -- but it is fine. I mean, it is --

(Simultaneous discussion.)

MR. CAPRON: Can't we say protocols?

DR. COX: I thought of that, Alex, but actually just leaving it protocols because it is a protocol for deriving but it is a research protocol for using but if we just say protocol and then say using versus deriving then I think it will be clear.

DR. HOLTZMAN: We cannot use research proposal because the research proposal does not use, it is the protocol described in them.

DR. COX: Just that one change, Harold, I think for me, at least --

DR. SHAPIRO: I understand. You want to make sure these are protocols and not just all the protocols around.

DR. COX: And whether we are -- when we are talking about deriving and when we are talking about using.

DR. HOLTZMAN: So in the first dot point after protocols you would put in for the derivation of ES and EG cells and then in third dot point at the end you would insert the words for the use of ES and EG cells?

DR. SHAPIRO: What is the second one? I got the first bullet.

DR. HOLTZMAN: The first one, right, is review of the protocols but if you go down to what have we asked it to provide to the agencies, is the principles relative to the review of the use protocols.

DR. SHAPIRO: Are you on eight or nine? Where are you?

DR. HOLTZMAN: I am on eight. There is three.

DR. GREIDER: The fourth bullet.

DR. HOLTZMAN: The third dot bullet.

MR. CAPRON: The third dot bullet should be brought into parallel with the language in eleven, which says research proposals utilizing ES/EG cells. They are providing advice to the sponsoring agency so we just use the same language. "For review of research proposals utilizing ES/EG cells."

DR. HOLTZMAN: Are we envisaging that the agency will receive proposals for protocols to derive, that it will review them themselves and then they will get, as it were, super review from this panel or does the review go directly to this panel?

DR. SHAPIRO: It has to go to the agency.

MR. CAPRON: IRB.

DR. HOLTZMAN: But does the agency review the protocol before it gets passed on to this group?

MR. CAPRON: That would depend upon the agency's own --

DR. SHAPIRO: Yes. Whatever the rules are. I could see it either way. Going at the same time. Going afterwards. Whatever. That is not critical.

MR. CAPRON: The derivation has to go to the national panel. That is the safeguard there. The safeguard on utilization was the sponsoring agency. I just was suggesting that we should use the same language as we do in recommendation eleven.

DR. HOLTZMAN: Okay.

DR. SHAPIRO: I want to just catch up here because I am behind here. The first bullet, someone was -- well, David pointed out, I think correctly, someone suggested words that read: "Reviewing protocols for the derivation of ES/EG cells and approving those." Is that -- that was the intention we have not been achieving.

Then there was another suggestion. Steve, you had one.

DR. HOLTZMAN: It is the third bullet point about the establishing requirements for the agency. I was asking whether the requirements and guidance with respect to use protocols or use and derivation protocols, okay, which raise the question of they would only need guidance on the latter if they were reviewing

the latter. What I think you folks answered is there may or may not be local agency review of derivation protocols.

What we are saying is whether or not there is, this oversight board does review derivation protocols and, therefore, I would agree with Alex's suggestion by the -- adopting the language of eleven of utilizing, all right, you appropriately gloss over both cases of when an agency does and does not review a derivation protocol.

DR. GREIDER: Where would you put the language?

DR. HOLTZMAN: Review of protocols utilizing -- right at the end of the dot point, right?

MR. CAPRON: Review of -- and then turn to the language from eleven, research proposals utilizing ES/EG cell lines.

DR. HOLTZMAN: Again I would use protocols because proposals do not --

DR. SHAPIRO: Let me get --

(Simultaneous discussion.)

DR. COX: This is a suggestion that is even simpler and maybe I am being too simpleminded here but the -- these -- you know, social and ethical issues, okay, pertain whether you are deriving them or whether

you are using them. They are different sets of social and ethical issues but they are social and ethical issues in either case. So simply in bullet number one it is the derivation but in bullet number three from my perspective it is the derivation and use.

DR. SHAPIRO: I actually like that idea because they are going to be see more protocols than anyone else from a wide variety of places and they are in a good position to do that because some of these are requirements and some of these are just guidance so they might issue some guidance.

DR. COX: So then it does not really change the language at all but it is just making clear that for like a simpleminded person when they are reading these are you talking about derivation or uses. So the first one is derivation and the third one is derivation and use.

MR. CAPRON: We do not want to use the word "proposals" you are saying. It should be projects or something.

DR. COX: I think "protocols" are fine because they -- for the reason that Steve said.

DR. SHAPIRO: The way I have got it written right now, and then we will work on it a little more

later but it is the review of research protocols deriving and/or utilizing ES/EG cells.

Other comments on -- I guess we will go back to nine now.

Carol?

DR. GREIDER: I was actually going back to eight since we looked at eight.

DR. SHAPIRO: That is fine.

DR. GREIDER: At the very beginning rather than starting off with the reason to make it parallel with the other recommendations, can we start after the comma and say, "The Department of Health and Human Services should establish a National Oversight and Review Panel to ensure that all federally funded --" put the subject first and then say why.

The other thing is maybe we should consider what we are going to call this because National Oversight and Review Panel, it does not say anything about what it is overseeing and reviewing, and if we are thinking about like RAC, RAC tells you what it is. If we could have something in the title. Whatever the other acronym was, was fine.

(Simultaneous discussion.)

DR. GREIDER: NORC or whatever.

(Simultaneous discussion.)

DR. GREIDER: I mean, the acronym is one thing but there is nothing in the title that tells you what they are overseeing and reviewing. I mean, a National Oversight and Review Panel could be for anything. It could be for, you know, sailing regulations.

DR. BRITO: National Stem Cell Oversight and Review Panel.

I had a comment about the sense right after that. The panel should have -- do we need to be more specific about the members of the panel because I have a concern here that including members of the public could make it so broad and general that you could wind up with a panel that is mostly scientists because you could have scientists or members of the public, or is this nonscientists?

DR. SHAPIRO: I was hesitant to start dividing this up and I thought the word -- my own reaction, Arturo, was that having broad multidisciplinary membership means you are going to have not just scientists but even lawyers.

(Simultaneous discussion.)

DR. SHAPIRO: And people like that.

(Simultaneous discussion.)

DR. SHAPIRO: To say nothing of economists and so on.

DR. GREIDER: And Canadians maybe.

(Simultaneous discussion.)

DR. SHAPIRO: Did you all see the paper this morning? It is hard to be a Canadian.

DR. DUMAS: Can I make a minor -- a very minor suggestion in that recommendation nine? In the statement?

DR. SHAPIRO: Recommendation nine?

DR. DUMAS: Yes.

DR. SHAPIRO: Okay.

DR. DUMAS: It starts, "In addition the panel --" I suggest changing the words "shall collect" instead of "should request."

DR. SHAPIRO: "Shall collect from sponsoring agencies."

DR. DUMAS: Right. It is more definitive and they may request them and not get them but what we are aiming at is that they collect these things and form a database.

DR. HOLTZMAN: That is great.

DR. SHAPIRO: Steve?

DR. HOLTZMAN: I am just endorsing that point.

DR. SHAPIRO: Jim?

DR. CHILDRESS: We refer to the reviewing protocols and approving those meet the requirements, and the public registry and then later under nine we talk about maintaining a list of certified cell lines but nowhere in these recommendations, eight and nine, and I am not sure that we do anywhere else either, do we say anything about the task of certifying. That is it is more than simply reviewing the protocols and approving those that meet the requirements.

That is actually -- that goes beyond that and unless we simply mean by that anything that is approved will be listed in the registry as certified. But I think that if we do not put something in the recommendations we really need to spend a fair amount of time in the text working out what is involved in certification because it does include, given our discussion yesterday, attention to those consent requirements.

DR. SHAPIRO: That is certainly right.

Kathi, then Carol, then Alex.

DR. HANNA: That was my question about the second bullet on eight. "Maintaining a public registry regarding ES and EG cells." That does not quite tell me what is in there and I was going to ask about has the

certification process been dropped. In a proposal yesterday there was a sentence about cell lines developed via approved protocols must be certified by the panel and then cell lines developed with nonfederal funds can be submitted to the panel for review and certification. And I was just curious in your conversations last night if you deliberately eliminated that.

DR. SHAPIRO: Alex?

MR. CAPRON: No, we had not and my thought was that that language really should have ended up in nine. And I realize, I mean, Jim, by reason of symmetry one might say, "Well, you would want it in eight and perhaps you ought to allude to it in eight." But, frankly, nine was the thing that we finally kind of stalled out on last night because we had this large paragraph which had represented a good discussion yesterday about the database and that just did not lend itself quite so easily to a bullet.

I do not like having these two bullets here and then having the paragraph and it seems to me that what we need to do is change, and maybe we can work on this during the break or something, change the clause that says, "The functions of which shall include," into

three sentences or three numbered subsections here describing each of them.

The record of the protocols needs at least the description, certification needs the language you just read, and the database needs what is here, and I think we just ought to try to massage them.

DR. SHAPIRO: I think that is right. I think that would work but I also think I agree with what Jim may have said that the second bullet above on eight, that is maintaining a public registry regarding ES and EG cells is not sufficient.

MR. CAPRON: Well, then what I think we ought to do is have between reviewing and maintaining a statement certifying cell lines that meet established ethical guidelines.

DR. SHAPIRO: We need something in addition to that.

DR. HOLTZMAN: Certifying cell lines that result from approved protocols.

DR. SHAPIRO: Sorry, Steve. I do not know where you are trying to put that phrase.

DR. HOLTZMAN: The second -- your second dot break after "reviewing." Your second function is "certifying cell lines that result from approved protocols."

DR. SHAPIRO: Certifying cell lines. Yes, that sounds like -- I wanted to go back to EG cell lines, human ES, et cetera, whatever the right way to --

DR. CASSELL: Wait, say that again.

DR. HOLTZMAN: Okay. The logic is the first one, they review the protocols. The third one is they are going to maintain a registry which we are going to describe further so in between they have a function of certifying ES and EG cell lines that result from approved protocols.

DR. SHAPIRO: Just adding an extra bullet.

DR. HOLTZMAN: It is an extra bullet between. They review, they certify and they maintain.

DR. SHAPIRO: Kathi and/or Eric?

MR. CAPRON: Well, that does raise an issue. Are they permitted to certify cell lines that result from protocols in the private sector generally that had met the criteria even though the research was not an approved protocol or only when a protocol has in advance been submitted and approved?

DR. HOLTZMAN: Well, in my vision of this -- and let's put aside grandfathering all cell lines for the moment. We will have to talk about that, right?

MR. CAPRON: Right.

DR. HOLTZMAN: Is what we are envisaging and encouraging is the private sector that if you want it to be certified you have got to submit your protocol.

MR. CAPRON: In advance.

DR. HOLTZMAN: In advance and it has to get approved just like the RAC.

MR. CAPRON: That is fine.

DR. HOLTZMAN: All right. Now whether we want to put up in its function -- I thought it was nicely -- by saying reviewing protocols as opposed to federally sponsored projects --

MR. CAPRON: Right.

DR. HOLTZMAN: -- it just was wide open.

DR. LEVINSON: You said that the panel would public members. If that is the case the meetings will be public. You have not said whether or not the protocols would be reviewed in a public session. If you are anticipating and encouraging the private sector to have their protocols for derivation reviewed they may or may not want to have that done in public and it may be proprietary. You could have provision for closing meetings for discussion of proprietary information.

MR. CAPRON: We have that under the Federal Advisory Committee's Act.

DR. LEVINSON: Right. But you haven't said anywhere about whether meetings and reviews will be conducted.

MR. CAPRON: Well, I do not think we have to -- we are not writing a statute here. If they -- if this panel is established under the Federal Advisory Committee's Act the proprietary information, personnel information and so forth can be kept private and executive sessions close to the public can be held for the discussion of that information provided that reports of what was done and we do not have to write that. That is the Administrative Procedures Act and a lot of other stuff. So I -- the only -- I mean, if you are saying should establish under the -- the panel should have broad membership and be subject to the Federal Advisory Committee's Act, fine.

My question went to the same thing that Arturo had raised about members of the public and it is from a different angle although you have highlighted it, Rachel. Reading it this way suggests that what we are saying is that it should not all be federal employees. That is sort of the way you are reading members of the public and, therefore, it is subject to the Federal Advisory Committee's Act.

We intended to mean people who are not specialists in any discipline but represent the public more broadly. I think that is what we meant by that. I think Rachel's reading is just as reasonable that what we are saying is in addition to -- that this would otherwise be a panel of federal employees not subject to open meeting laws because those are just federal employees meeting to do their job.

I think we anticipated both, that it would be both a panel made up of -- not of federal employees but of members of the public and that "members of the public" in the second sense means nonspecialists. I think we better use language to convey that because I -- it is confusing.

DR. MESLIN: In the recommendation itself.

MR. CAPRON: Well, if we want to say broad multidisciplinary including nonspecialists or including members of the public who are not specialists, that at least says why we are using the phrase or something.

DR. SHAPIRO: Steve?

DR. HOLTZMAN: I think we can find the language in various statutes or whatever which create these things and things like how to establish an animal -- institutional animal care and use committee,

you can find language there and we could come up with it.

I think Rachel makes an important point which is an opportunity for us not in recommendation language but in explanatory language, and that is when we get to the recommendation where we are exhorting the private sector to use this under it we could talk a little bit about, for example, the RAC experience and how there is provisions in federal law that allows for the sensitive disclosure and confidentiality, and it did not impede that in the past, and we envisage that here as well.

DR. SHAPIRO: Okay. Thank you very much. That is very helpful.

Diane?

DR. SCOTT-JONES: I have a suggestion for the material that is in the paragraph at the end of recommendation nine. In reading all of this over it seems that that is another function of the panel and should be in recommendation eight and it could come after the bullet that says maintaining a public registry.

And if you use the same form it could read something like collecting from sponsoring federal agencies and then the rest of the language could be the

same. It could end with this database will be linked to the public registry and that last part of the sentence could be put in the explanatory material that would be outside the actual recommendation because it seems a little bit out of place in that it specifies a function of the panel but instead of being in recommendation eight along with the other functions it is just tacked on at the end of recommendation nine.

DR. SHAPIRO: Alex?

MR. CAPRON: Yes. Diane, this may not have worked out. We may just be better off collapsing eight and nine but the thought was that we would simply allude to the registry in recommendation eight and actually describe the three parts of the registry, the record of the protocols, the list of certified cell lines, and the database of results, and explain those in nine because it became too complicated to try to shovel all that up under the bullets in eight, which is what you are trying to do, put it back up there.

As I say, it may --

DR. DUMAS: Why don't you make it a third bullet under nine.

MR. CAPRON: Yes, it should be. All of nine has to be rewritten.

DR. SCOTT-JONES: Then I would say that would be fine. It just seems out of place and it is introduced as another function of the panel and just that manner of introducing it makes it seem more appropriate for eight. So I would say it would be equally appropriate just to make it another bullet under nine.

DR. SHAPIRO: If we started with "collect" for example.

MR. CAPRON: Yes, exactly. Collect a database.

DR. SHAPIRO: In addition, the panel --

MR. CAPRON: Yes, exactly. But remember that is where we broke down last night and we sort of said massaging that paragraph to be parallel to the others was just beyond us at 11:00 o'clock.

DR. SHAPIRO: Lucky we do not have a videotape of how we all looked at 11:00 o'clock last night.

DR. SCOTT-JONES: You could just say something like establish a database to be linked to the registry and then say a little bit more from the other sentences about what the database would include.

DR. DUMAS: Yes.

DR. CASSELL: Wait a minute. Where do you say that?

MR. CAPRON: As another bullet under eight.

(Simultaneous discussion.)

DR. CASSELL: As long as it is part of the recommendation and not part of the text.

DR. SHAPIRO: I promise, Eric, this point is going to be in the recommendation and it will stay there. We may readjust it here a little bit but it will be in part of the record.

Okay. Any comments on eight and nine?

Recommendation ten reads as follows: "Human subjects regulations should be revised as necessary to make clear that protocols involving the derivation of ES/EG cells must be reviewed and approved by an Institutional Review Board prior to consideration by the National Oversight and Review Panel. IRB's should ensure compliance with any requirements established by the panel, including confirming that institutions in the U.S. or abroad which supply embryos or fetuses have obtained them in accordance with the requirements established in the panel."

DR. DUMAS: I have --

DR. SHAPIRO: Yes, Rhetaugh?

DR. DUMAS: I think you have got two recommendations folded there and I would suggest that beginning with "IRB's should" make that a separate recommendation because it refers to the -- to an aspect that has not been formally mentioned before and it has to do with international issues and I think it ought to be separated out.

DR. SHAPIRO: I have no objection to that. Okay. Any other issues on ten?

Recommendation eleven: "When reviewing research protocols using ES/EG cell lines all federal agencies should ensure that their review processes comply with any requirements established by the National Oversight and Review Panel (see recommendation nine) paying particular attention at the adequacy and the justification for using such cell lines." So I think this is something we have talked about over and over again.

DR. HOLTZMAN: Just to make sure, you said protocols instead of proposals, do we agree we are making that change? I think we thought that was obvious.

DR. DUMAS: Protocols.

DR. HOLTZMAN: That is actually what you said, Harold.

DR. SHAPIRO: That is what I use all the time, Steve --

DR. HOLTZMAN: No, I think proposals does not work so I just wanted to confirm that.

DR. SHAPIRO: I agree with protocols.

MR. CAPRON: I tried to use protocols yesterday and was told by Eric that that only referred to --

DR. DUMAS: Come on.

(Simultaneous discussion.)

DR. COX: It is complicated but overall, I agree with Steve, using protocols is a safer --

DR. HOLTZMAN: My next question is do we need the "paying particular attention to the adequacy?"

DR. SHAPIRO: Well, do we need it? This again just reflects -- I mean, yes and no is the answer. It reflects the concern of many that we -- it is just the principle parsimony as Alex said yesterday.

MR. CAPRON: Unextravagance.

DR. SHAPIRO: Unextravagance is what I said. Parsimony is actually better. So I think that should be used.

Recommendation twelve: "For research on ES/EG cells that otherwise would be eligible for federal funding NBAC encourages privately funded researchers and

private sponsors voluntarily to adopt the recommendations of this report that apply to such research, including submitting reports of protocols for review to the National Oversight and Review Panel."

This is a recommendation trying to articulate an encouragement to the private sector to use the system if they wish to.

Alex?

MR. CAPRON: You know, I have a sense that we need to put privately funded before research at the beginning of that or really --

DR. DUMAS: I agree.

MR. CAPRON: -- otherwise you are reading along and you say "otherwise be eligible," why be otherwise.

DR. SHAPIRO: Excuse me. What is the suggestion again?

MR. CAPRON: Putting the words "privately funded" before "research" at the beginning of the paragraph.

DR. SHAPIRO: Privately funded research on ES/EG cells.

MR. CAPRON: Would otherwise be eligible for federal funding.

DR. HOLTZMAN: You could just say the researchers -- you could say researcher and sponsor.

MR. CAPRON: Yes.

DR. SHAPIRO: As you look at recommendation twelve, let me also read out recommendation thirteen because they compliment each other because recommendation twelve deals with research that if -- that would be eligible for federal funding. Thirteen deals with research that would not be eligible for federal funding but these occur in the private sector. So let me also read recommendation thirteen and then we will come back to the change in twelve.

MR. CAPRON: And add the adjectives.

DR. SHAPIRO: Recommendation thirteen currently reads: "For research projects that involve deriving ES/EG cells that would not be eligible for federal funding under recommendations three and four in this report NBAC recommends that: (A) professional societies and trade associations should develop and promulgate ethical safeguards and standards consistent with the principles underlying this report; (B) privately funded researchers conducting this research and their sponsors should voluntarily comply with these standards." That is the ones established under (A), not

the standards in the report but the ones which hopefully will be similar.

Those are just two. It is an attempt to look at privately funded research. One that would be eligible in one case and is not eligible in our recommendations in another. So let's now go back to twelve.

MR. CAPRON: Well, I think Steve is right. We can actually drop "privately funded" and the word "private" from the clause beginning NBAC encourages so it would say "For privately funded research ES --" are we using ES slash or ES and or whatever we come up with? "-- ES/EG cells that would otherwise be eligible for federal funding NBAC encourages researchers and sponsors voluntarily to adopt."

Down below I would -- and we should do the same thing in recommendation thirteen, which is now recommendation fourteen after Rhetaugh's suggestion. And we should, I believe, under (A) put the word "and" between "ethical safeguards and standards" and then use the phrase "safeguards and standards" in (B) and that makes it much clearer that we are referring to (A).

DR. DUMAS: (B) is "safeguards and standards."

DR. SHAPIRO: Okay. I am sorry. I am just trying to -- Steve, and then Diane.

DR. HOLTZMAN: I believe but this is a question also that twelve is really making reference to protocols for derivation, not protocols for use.

(Simultaneous discussion.)

DR. HOLTZMAN: You are saying --

DR. DUMAS: The use because it would otherwise be approved by the -- it could be derivation and use otherwise approved for federal funding.

DR. HOLTZMAN: Okay. Then -- okay. If we mean it generally in the preamble, the first part, it can be broad. I think then in the second half when we are talking -- submitting protocols for review, the only protocols that are for the derivation. Okay.

MR. CAPRON: Correct.

DR. HOLTZMAN: Okay. Now I know one -- a careful reader of the report would know that at this point having read it from beginning to end but most readers jump right to the recommendations, right, and I think this is a place where there is a virtue in actually saying "protocols for the derivation of."

DR. COX: Actually I do not agree with that because --

DR. HOLTZMAN: Only in the second part, not the first part where the protocols --

DR. SHAPIRO: No one else has to submit these protocols here for review to NORP so there is no reason, I think, why the private sector should have specially --

DR. DUMAS: Right.

DR. COX: On the other hand, for nonproprietary uses the database is collecting that information so --

DR. HOLTZMAN: The first part of this says that.

DR. SHAPIRO: It is just the review. That is it is not the database. It is just the review, which I think none of us want --

MR. CAPRON: And we are adding the phrase "for the derivation of ES/EG cells" after the protocol on the fourth line of --

DR. DUMAS: I suggest you put a period after "report that apply to such research" and make a new sentence so it will not be confusing about this review of the protocol.

DR. SHAPIRO: And say this includes if you want --

DR. DUMAS: Huh?

DR. SHAPIRO: You want to put a period and say "this includes."

DR. DUMAS: Yes. This includes or they are encouraged to submit protocols.

DR. SHAPIRO: These are protocols that involve the derivation.

DR. DUMAS: Right.

DR. COX: Yes. It is still not clear to me, though, where it is clear that we are encouraging information about the use, also.

DR. SHAPIRO: It is adopting the recommendations of this report.

DR. HOLTZMAN: We can say adopting recommendations and providing information. I mean, we could try providing some information or you could explain out in the text about providing the information to the registry, et cetera, in the database.

MR. CAPRON: We already have -- and this would be maintained in recommendation nine that the private sector is encouraged to submit similar -- we cannot shove everything into --

DR. COX: Alex, that is the part that I was missing -- thank you. Sorry. Never mind.

DR. SHAPIRO: Any comments beyond the ones already given on recommendation thirteen?

Diane? Excuse me, Diane. I should have recognized you before. I had you on my list and I forgot.

DR. SCOTT-JONES: This is very minor. For recommendation thirteen I think we should omit the word "should" from (A) and from (B) simply because it reads better to say "NBAC recommends that professional societies and trade associations develop."

DR. SHAPIRO: That is correct.

MR. CAPRON: You said (A) and (B).

DR. CASSELL: Take the "should" out.

DR. SHAPIRO: That is right. I agree.

Here is recommendation fourteen -- I am sorry. Bette and Steve?

DR. KRAMER: Can I go back to ten? There is something about ten that is bothering me. Tying the protocols about derivation and use of ES/EG cells into human subjects regulations is bothering me. Does that create an opening for an allegation that, in fact, we consider these embryos, these spare embryos to be human subjects?

DR. SHAPIRO: This is an issue which has -- you are quite right -- come up over and over again, which is why we have avoided doing anything regarding subpart A and subpart B and so on but we want to use an

existing review mechanism that is available. This is what we are doing here in my estimation.

DR. KRAMER: I am really bothered by this terribly.

MR. CAPRON: Well, if we were to say it should be clear that they are under the jurisdiction of the IRB's that would have the effect that you are suggesting that we are somehow suggesting they are living individuals but remember we are talking about what this says is derivation.

It is not use and at the point of derivation, although there is some ambiguity, if you are dealing with human embryos the argument that you are under 45CFR46 is very strong in the way that the department has thus far interpreted part B that all research involving embryos is encompassed within the phrase "IVF" or in vitro fertilization, research on the development of in vitro fertilization.

If you go back to the introductory language when it was published in the Federal Register they did not say that but they have interpreted it that way consistently for the last 15 years.

DR. GREIDER: So could we have language to that effect?

MR. CAPRON: In the explanatory text.

DR. GREIDER: Explanatory.

MR. CAPRON: We could say because the recovery is not clear precisely because, you know, of the thing that concerns you --

DR. KRAMER: Well, first of all -- well, that is first of all but second of all isn't it -- for it to be reviewed by an IRB if it is already -- if it is going in -- after that go on to this other -- why is --

MR. CAPRON: IRB's review -- recombinant DNA protocols are reviewed by both IRB's and human biological materials committees at institutions before they go on to the RAC.

DR. HOLTZMAN: Those are for gene therapy.

MR. CAPRON: For gene therapy, yes. Excuse me.

(Simultaneous discussion.)

DR. SHAPIRO: It is duplicative in the sense that more than one group is looking at it. The idea was that we needed some national -- both local and national review here becasue of the special nature of this kind of materials and the concerns that are associated with it. That is my -- at least that is my view.

Steve and Diane?

DR. HOLTZMAN: So earlier we had a discussion about use protocols would not be looked at by IRB's.

DR. SHAPIRO: Right.

DR. HOLTZMAN: Now we are coming to the derivation protocols, and I know I tend to confuse in my head when I think about derivation I think about intervention with the woman who is donating the oocytes, which is clearly human subjects, but -- and I think it just is worth a pause to think about the woman could have donated the oocytes and downstream the embryos coming out of the freezer. My question is when those things are currently used, taken out of the freeze to, for example, make a DNA library, is that subject to IRB review?

MR. CAPRON: Cannot be federally funded.

DR. HOLTZMAN: Cannot be federally funded. A good point.

MR. CAPRON: We are saying it should be federally funded and we are saying because it is now federally funded it should be treated like other protocols that involve human organisms. Now whether they qualify under part A as a living individual or not, they qualify under B, which covers in vitro

fertilization which is taken to include any manipulation of the embryo.

DR. DUMAS: Would it be more politic (sic) to cite the legislation instead of calling it human subjects? Cite the legislation and say should be revised.

DR. SHAPIRO: I think none of us have suggested that we define this as being a human subject as currently defined. No one has suggested that. That is not either desirable or appropriate. And the real question is, and we do not want to say anything that would indicate that we do believe it is a human subject.

We could, in principle, side step the IRB all together and develop another -- I do think we need local review in the derivation case, not in the use case. So we could develop and ask them to put up another committee. Now the idea was to try not to do that. There is some ambiguity as to just how over the long stream of time here part A and part B are going to be interpreted whether or not to include this.

I am myself a little hesitant to start going to recommending language in the Common Rule because that seems to buy into this human subjects thing which I do not want to do. So I think of this myself as, yes, some of these things may be covered. If they are, they are.

We are not saying anything about that. If not, there is a local group that is used to dealing with research protocols which can review and we are in that level hijacking that group to do this. To me, that is preferable to establishing a new set of groups which will have new rules and so on and so forth.

(Simultaneous discussion.)

DR. SCOTT-JONES: Most of what I wanted to say has already been said by the there or four people who have spoken but the one last thing that I had to say that I wanted to say in response to Bette's concern about redundant efforts between the local IRB and the National Oversight and Review Panel, I think we should keep in mind all the layers of review of research, and most institutions would want to maintain their own review, whether we wrote it in our recommendations or not just because they want to maintain that. Even within a university a department may have reviews of research conducted that is not required but they would like to do that before it goes to the IRB out of their department so that is the reason for it. It is not to prevent redundancy or to have redundancies because universities would want to do that anyway.

DR. SHAPIRO: Bette?

DR. KRAMER: If the university wanted to do it that is a matter of internal policy and let them do it if that is the way they want to do it but as between a particular institution electing to do something in a certain mode and our requiring it, I think that is two very different things.

I am not at all satisfied that it is really necessary for it to be reviewed by an IRB when it is going to be reviewed by a national body which is obviously going to have more informed oversight on these than a local body. I do not -- and I am really disturbed by it. You know, I think we have just got to get it out of that --

DR. SHAPIRO: Let's just -- I understand the point -- perspective. I certainly understand the perspective but let's just see where we stand on it because we really -- I do not want to spend a lot of time on this but we can be for it or against it, and I think there is very good reasons on both sides so let's just see how many of us would like to keep this as it is, that is requiring local IRB review in this derivation -- in the derivation case? Okay. So we are --

DR. BACKLAR: I have to go but could I just say that I felt that what Rhetaugh suggested was very

good, that instead of saying "human subject regulations" refer to the regulation 45CFR, however you want to do it.

DR. GREIDER: I actually suggest an even stronger revision of that and to start with institutional review board review or review by an IRB should be -- these protocols should be reviewed by an IRB. Rather than starting off with something about changing regulations, what do we want to say? We want to say that these protocols should be reviewed by an IRB.

DR. SHAPIRO: We will either do that or something like that as we -- or eliminate the reference to human subjects regulations and say something like federal policy or something like that.

DR. BACKLAR: Right.

(Simultaneous discussion.)

DR. SHAPIRO: Yes, keep the concerns that have been expressed all around. Okay.

Let's go to the last one and then we are going to take a break as we try to rewrite this. This is one we did not deal with at all yesterday and it reads as follows:

"The National Oversight and Review Panel and the public registry described in recommendations eight

and nine..." I am not sure that is correct anymore but it may be, yes. "...should be sunset after a period of five years and the process and substance of their activity independently evaluated to determine whether these mechanisms have adequately performed their functions."

DR. CASSELL: Do we have to use the word "sunset."

(Simultaneous discussion.)

DR. SHAPIRO: All right. Yes, Alex?

MR. CAPRON: Could I take us back to recommendation -- the second sentence of recommendation one just for a second?

DR. DUMAS: Are we finished with fourteen? Are we all done with that one?

(Simultaneous discussion.)

DR. DUMAS: Okay.

MR. CAPRON: It now says, "In addition, existing statutory and regulatory provisions should be amended to include the derivation and use of EG cells for research purposes." I think I may have written that so I am not criticizing somebody else. It just falls flat to me. Let me try an alternative.

"In addition, relevant statutes and regulations should be amended to make clear that

existing ethical safeguards apply to the derivation and use of EG cells for research purposes.

DR. GREIDER: Great.

(Simultaneous discussion.)

DR. SHAPIRO: Okay. What I would propose now, I have made some -- at least some writing assignments.

Steve, I have asked you to --

DR. HOLTZMAN: I gave them to her already.

DR. SHAPIRO: Do you know about any outstanding ones because I want to ask staff to sit down and create a new set and pass them out to us.

DR. DUMAS: I want to commend the late hour work last night.

(Applause.)

DR. CASSELL: Well, I want to point out that if we took away the abbreviations we would add only eight words and people would know that we were talking about an embryo and know that we are talking about stem cells instead of whatever ES stands for.

DR. SHAPIRO: I will take that under advisement.

DR. CASSELL: I know it will not help.

(Simultaneous discussion.)

DR. SHAPIRO: David?

DR. COX: This is a very minor point but it is for consistency. In some places we make clear we are talking about human and in other places we do not put it, and in the context of the animal stuff I would hate, you know, for that to be ambiguous.

DR. SHAPIRO: That is a good point. In fact, in the text we have got a lot of things to do of that nature to make it consistent everywhere in the text.

DR. COX: The text is one thing. These recommendations, I think we need to really try and have --

DR. SHAPIRO: All right. Let's adjourn for 20 minutes.

(Whereupon, a break was taken.)

DR. SHAPIRO: Okay. For those of us that are still here let's review these recommendations once again. I am sure we have not got it all right but I am determined --

DR. DUMAS: Not perfect.

DR. SHAPIRO: Not perfect but I am determined --

DR. DUMAS: It is all right.

DR. SHAPIRO: -- to get enough of it done here so we know what changes to make and pass out to you

by e-mail in the next day or so. So let's just go through them.

I am going to read them once again and see if they either failed or succeeded in reflecting our conversation this morning.

Recommendation one: "Researching involving the derivation and use of human embryonic germ cells from cadaveric fetal tissue should continue to be eligible for federal funding. In addition, relevant statutes and regulations should be amended to make clear that existing ethical safeguards apply to the derivation and use of embryonic germ cells for research purposes."

Okay.

Recommendation two: "Research involving the derivation and use of human embryonic stem cells from embryos remaining after infertility treatments should be eligible for federal funding. An exception should be made to the present statutory ban on federal funding of embryo research to permit federal agencies to fund research involving the derivation of human embryonic stem cells from this source, under appropriate regulations that include public oversight and review."

Three: "Federal agencies should not fund research to generate or use human embryonic stem cells derived from embryos made via IVF..." we will come back

to that in a minute. "...solely for research purposes." Let's not worry about IVF. There is a controversy about whether we should acronyms or spell them out and so on. Let's not worry about this right now.

MR. CAPRON: We should have a knock down, drag out about that.

DR. SHAPIRO: Yes, that is right. After I leave you can -- those who are interested can use the center ring here.

DR. GREIDER: Mud wrestling.

DR. HOLTZMAN: Do you want to do wordsmithing as we go through this or not?

DR. SHAPIRO: Just mark up your copy and give it to Kathi because I do -- if we can all -- I want to save some time, if we can, for the international so I really appreciate any comments and I should make -- ask all the people who have sort of marked up copies of the complete draft to please give them to the staff so as we rewrite text we can incorporate your ideas and so on.

Recommendation four: "Federal agencies should not fund research to generate or use human embryonic stem cells derived from embryos made via somatic cell nuclear transfer into oocytes solely for research purposes."

It is interesting that we eliminated the words under three and eliminated the acronym under four but we will have to get that all straightened out and complete.

Okay.

Recommendation five: "Prospective donors of embryos remaining after infertility treatments should receive timely, relevant, and appropriate information to make an informed and voluntary choice regarding disposition of the embryo. Prior to considering the potential research use of the embryos, the prospective donor should have been presented with the options of storing the remaining embryos, donating them to another woman, or discarding them. If the prospective donor chooses to discard the embryos, the options of donating to research may be presented during which presentation the person seeking the donation should:"

And here are what follows the should colon. Okay.

"Disclose that the embryonic stem cell research is not intended to provide medical benefits to the donor,

"Make clear that consenting or refusing will not affect the quality of any future care provided to the prospective donor,

"Describe the general research area and the specific research protocol if known,

"Disclose the source of funding and expected commercial benefits of the research,

"Make clear that embryos used in research will not be transferred to any woman's uterus, and

"Make clear that the research will involve the destruction of the embryos."

Okay.

DR. HOLTZMAN: Harold?

DR. SHAPIRO: Yes.

DR. HOLTZMAN: I do not know if this is substantive or not. Under the "disclose the source of funding," I think we need an "if known."

DR. GREIDER: I think so, too. "Of the research," we can put "if known" at the end.

DR. _____: Why wouldn't that be known?

DR. HOLTZMAN: Why wouldn't that be known? Because in an IVF clinic I know there may be research protocols downstream, the woman has discarded, I say may I use this in future research. I do not know who the sponsor is going to be and she just consents.

DR. SHAPIRO: Kind of banking those --

DR. HOLTZMAN: A research bank, that is right.

(Simultaneous discussion.)

DR. GREIDER: After the research.

DR. HOLTZMAN: I would use the same formulation in the previous one with "if known" at the end.

DR. GREIDER: Okay.

DR. SHAPIRO: Six: "In federally funded research involving embryos remaining after infertility treatments, the donor may not restrict the patient-subjects who will receive the cells derived from the embryos." The commentary is just a place holder to remind us to deal with the commentary on this to draw the parallels we have talked about.

Recommendation seven: "Cadaveric fetal tissue and embryos..." we have to choose between "should" and may "...not be bought and sold.

I think it was Eric that wanted us to use "may" rather than "should."

DR. KRAMER: We want to use whatever is the stronger.

DR. CHILDRESS: In statement of principle I think we ought to use "should."

(Simultaneous discussion.)

DR. COX: We do not have the force of law.

DR. SHAPIRO: That is right. That is my own view also since we are not writing laws. Somebody is going to have to write these regulations if they accept these.

Recommendation eight, which is now longer and I am sure we are going to have to review, there is a number of issues that I want to bring up here, and we have to probably decide whether to keep eight and nine together again or what, but anyhow let me just read eight as it stands.

"The Department of Health and Human Services should establish a National Oversight and Review Panel to ensure that all federally funded research involving the derivation and use of human embryonic stem cells and embryonic germ cells is conducted in conformance with the ethical principles and recommendations provided in this report. The panel should have a broad, multidisciplinary membership, including members of the public. The responsibilities of the Panel shall include:"

And here there are a number of bullets, indeed there are about seven of them.

"Reviewing protocols for the derivation of human embryonic stem cells and human embryonic germ

cells and approving those that meet the requirements described in this report."

Two: "Certifying ES/EG cell lines that result from approved protocols."

Three: "Maintaining a public registry of approved ES/EG cell lines."

Could we use "certify" instead of "approved" there because they just talk about certifying them? Okay. So I am going to put "certify" in there.

MR. CAPRON: The public registry has three functions, which is why we use the word "regarding" before. It has the function of "approve protocols, list of certified cell lines, and data bank." So if we say "maintaining a public registry of approved --" it is not an accurate description. What we said before it was revised was maintaining a public registry regarding ES and EG cells, see recommendation --

DR. SHAPIRO: I did not really like that. I mean, I understand what you said. That seemed to me -- I could understand what it meant, a registry regarding ES/EG cells. I just could not understand what it meant. I understand you can go to recommendation nine but I wanted something in there which had something more informative in it than just regarding ES.

MR. CAPRON: I mean, if we had a name for it, if it shall maintain the public registry of ES/EG cell research, I mean that would --

DR. HOLTZMAN: Could we say, to get both of your points, "maintaining a public registry of certified ES/EG cell lines and related information, see recommendation nine."?

MR. CAPRON: Sure. But yesterday people said it was just as important to have the registry be of approved protocols and --

(Simultaneous discussion.)

DR. HOLTZMAN: But that will be sculled out in --

DR. SHAPIRO: Jim, and then Diane.

DR. CHILDRESS: It seems to me to be useful to have here following the previous bullet about certification an indication that they will be maintained as a public registry the certified cell lines so we just might put "maintaining a record of certified ES/EG cell lines in the public registry," and see the recommendation for the other functions.

DR. SHAPIRO: Eric, and then Diane.

DR. MESLIN: What if you inverted the second and third bullet since following Alex's logic the public

registry is the thing you are describing and then you could list the bullets that follow.

DR. SHAPIRO: You are describing the responsibilities of the panel.

(Simultaneous discussion.)

MR. CAPRON: And all I am saying is what if we gave it a name for the moment and just said the public registry of ES/EG cell research or human ES/EG cell research as though that were the name of it, see recommendation nine, and that is what recommendation nine deals with. I just do not want to over emphasize one function over another.

DR. DUMAS: I am trying to understand what the problem is.

DR. SHAPIRO: Okay, Diane?

DR. SCOTT-JONES; We could simply say in the third bullet "maintaining a public registry of approved protocols and certified ES/EG cell lines, see recommendation nine."

DR. SHAPIRO: And the bank of --

DR. SCOTT-JONES: The data bank is now in eight instead of in nine. The database is now in eight instead of nine.

DR. SHAPIRO: It seems to me that we can -- I would like to use the word "certified" here in this

bullet and I think somebody mentioned "and related information." That may be broad enough to include both the protocols and everything else that would be in here. So let's just use that here. I do not --

DR. DUMAS: It is certifying cell lines that result from approved protocols and --

MR. CAPRON: It is the next one. "Maintaining a public registry of certified ES/EG cell lines and related information."

DR. SHAPIRO: Jim had a slightly --

DR. CHILDRESS: I think Steve's -- the direction we are going in, I think it would be Steve's recommendation, the wording.

DR. HOLTZMAN: Yes, that is what Harold just did.

DR. SHAPIRO: So would you say it again, Steve?

DR. HOLTZMAN: "Maintaining a public registry of certified ES/EG cell lines and related information, see recommendation nine." We are hanging up on the fact that registry we want to --

DR. SHAPIRO: Let's go through this. Let's get on with this and we may come to --

MR. CAPRON: It works.

DR. HOLTZMAN: Yes, it works.

DR. SHAPIRO: Fourth here: "Collecting from sponsoring federal agencies descriptions of all protocols that use or derive such cells with any available information concerning research outcomes, including published papers. The private sector is encouraged to submit similar, nonproprietary data."

Five or the fifth bullet: "Establishing a database which should be linked to the public registry to be used by the panel to track the history and ultimate use of certified cell lines for the purpose of policy development."

The next bullet: "Establishing requirements for and provide guidance to sponsoring agencies on the social and ethical issues that should be considered in the review of research protocols that derive or use such cells."

The last bullet here: "Providing an annual report to the DHHS Secretary which would include an assessment of the current state of the science for both derivation and use of embryonic stem cells and embryonic germ cells, a review of recent developments in the broad category of human stem cell research, a summary of any emerging ethical or social concerns associated with this research, and a review of the adequacy and currency of the recommendations addressed in this report."

MR. CAPRON: May I make a comment?

DR. SHAPIRO: Yes.

MR. CAPRON: I think that the way this has been revised, which is fine, has obliterated the need for recommendation nine and that we ought to take any thoughts about nine not fully encompassed and just put them in here so that we are going to say we are going to maintain a public registry.

DR. DUMAS: I agree.

DR. SHAPIRO: I agree with that. The way this has worked out I think that is right so we will put nine and ten and merge those two points that are left in there, two bullets which are really small bullets, will be incorporated.

MR. CAPRON: I mean, actually the second bullet is already in.

DR. DUMAS: This one, too. The second is two.

MR. CAPRON: Why don't we simply say maintaining a public registry of approved ES/EG protocols and certified cell lines because that is now what it does.

DR. SCOTT-JONES: I suggested that precisely.

(Simultaneous discussion.)

MR. CAPRON: Diane, I did not --

DR. SCOTT-JONES: You just did not know you were going getting around to --

MR. CAPRON: I thought that we had said the registry has three components. A list of certified cell lines, record of the approved protocols, and a database. As it is written here now, which is fine, the database is something separate, which is related or linked to.

DR. SCOTT-JONES: Right.

DR. SHAPIRO: So we --

DR. SCOTT-JONES: That is my point.

DR. SHAPIRO: So we can incorporate that in.

DR. HOLTZMAN: So point three is now going to read "maintaining a public registry of approved protocols certified --"

DR. SHAPIRO: "Certified ES cell lines."

MR. CAPRON: And that is in.

DR. SCOTT-JONES: That is the end.

MR. CAPRON: And the database is covered by the other --

DR. SHAPIRO: All right. Then, Diane, thank you very much. We wish we understood -- got to you earlier and faster. We apologize.

DR. DUMAS: You got it.

DR. SHAPIRO: Okay. We will use the numbers that are still on here although obviously it is going to be -- have to be renumbered.

MR. CAPRON: One thing which would come closer to making clear what we mean is to put the word "general" before "public." "Including members of the general public."

DR. SHAPIRO: That is a good point, I think.

MR. CAPRON: That is, I think, a phraseology that is used to suggest the --

DR. SHAPIRO: We will do that. Okay. Let's now go to what on this is recommendation ten. As I said all these will change a little bit. This is a change which I made for purposes of clarifying our discussion. We need to absolutely discuss this.

We had some discussion before. First of all, ten is broken -- what was one recommendation is now broken into two. I was trying to think through the issues that we raised surrounding Bette's comment that we need a local IRB review, are we going to fuse this with human subjects review? We are uncertain about B, subsection B applies and so on.

So this is one possibility here and you may or may not like it but I recognize it is a change and so

let's just -- let me read it and then we will discuss the substance of it.

Protocols involving the derivation of embryonic stem cells and embryonic germ cells must be reviewed and approved by an appropriately constituted and convened local review body prior to consideration by the National Oversight and Review -- well, that is not quite right either anymore because -- it is. It is. Excuse me. It is. It is derivation.

DR. HOLTZMAN: It should be "should" instead of "must."

DR. SHAPIRO: I beg your pardon. Oh, "should," yes.

MR. CAPRON: We had "must" before.

DR. SHAPIRO: Let's discuss -- first of all, before we get to "should" or "must" let's discuss the issue here. Now the issue is -- and the reason I wrote -- asked that it be written this way is written this way it has the advantage of focusing on the fact that you require local review. That is the substance of it. And people would be free to use their IRB's or, if not, some other appropriately constituted group. That is a possibility.

I am really quite committed to the local review and I could easily myself -- although this is not

a big matter of principle, I just want to put the matter before us as to whether we want to stick with the IRB's or not and I, frankly, do not have -- I am not going to fight a lot for that.

David, Laurie, and then Diane.

DR. COX: So with respect to the last question you asked I like having it ambiguous and say local review and let people do what they want in that context. I would say, though, that something else has to be added to this because the first question I would ask if I was a local person is to what end do you want local review and so to have in there that you want local review to ensure that these follow the standards set by the national body. What are you trying to be sure of?

DR. SHAPIRO: So then it comes in the recommendation. That is the recommendation right after that. That used to be two. It used to be a single recommendation. We have broken it in two. But if you look at eleven -- we will come back to the local review situation. It does say that the -- this body should ensure compliance, which is exactly, I think, the point you were making.

Laurie?

DR. FLYNN: I guess I am not understanding why we would not want to go ahead and name the IRB. We

know what IRB's are. We know that kind of requirements there are for the constitution and structure and ongoing work of IRB's. I worry that an appropriately constituted and convened local review body may not ensure the sort of transparency for this process that I think is critical. So I am very much in favor. Understanding the concerns but very much in favor of charging this to the IRB and all -- with all of its attendant pluses and problems.

DR. DUMAS: I am, too.

DR. SHAPIRO: Okay. Diane?

DR. SCOTT-JONES: I am also not clear on why it would be inappropriate to say the IRB and I think someone reading this might think that the intent is to suggest that there be another local review body instead of the IRB so I suppose I would be -- I did not have problems with saying IRB. I do not know if it would help whatever other concerns there were to say reviewed and approved by an IRB or other appropriately constituted and convened local review body. I am just not clear on what fellow commissioners saw as the problems.

DR. SHAPIRO: Back up and let's see what other views are. Bette and then Alex, and then Jim.

DR. KRAMER: One possibility, of course, is that a particular institution might have a body within a specific department that they would consider would be an appropriate review body. I would request that the language of the recommendation itself not specify IRB, whether it does or it does not, that in the explanatory text that whenever we -- if we make reference to the IRB that we include words like "despite the fact that this is not human subjects." I mean, that we make clear that we do not -- just to clarify that point.

DR. SHAPIRO: Alex?

MR. CAPRON: Well, if we were to do something of the sort that Bette wants or if we are going to use the language that you have suggested, I think we have to mount a full defense of why we want to waive or change the present human subjects regulations. Like it or not, subpart B of those includes embryo research and this -- the derivation process using embryos is embryo research so we would have to explain why having the Department of Obstetrics or the Department of Embryology or something else for all the reasons Laurie just cited, a group that we do not know how it is going to be "appropriately" constituted is preferable to an established group that under present regulations does not have -- I do not -- I have never

heard any discussion in this commission of what that language would be like. So I am with Diane in thinking that it should be -- and Laurie in thinking we should say IRB.

DR. SHAPIRO: Carol?

DR. GREIDER: I was going to ask Steve to reiterate what he had mentioned about the issues of human subjects and the current --

DR. HOLTZMAN: Well, as Alex has pointed out to me and showed me the materials that have been written and some papers, CFR -- the CFR itself, subpart B is at best ambiguous and it says in vitro fertilization is controlled. There is a subsequent regulation issued by DHHS in '94 which says that includes research on the embryo. Okay. Which is what Alex is pointing to when he says, "The reg says." Alex is not saying that subpart B on its face says that. It is rather that DHHS has interpreted it and apparently has the legal authority to interpret.

DR. SCOTT-JONES: Yes.

(Simultaneous discussion.)

DR. HOLTZMAN: We are without a license here. Okay. Now --

MR. CAPRON: They have such a license.

DR. HOLTZMAN: Okay. One argument -- some of us believe that it is -- there are more global reasons for why you would not want to be seen as endorsing that interpretation of the reg, which is I think maybe what Bette is pointing to in terms of saying we do not want to say that that thing is a human subject. I think Pat was making that point as well.

We also in various parts of our deliberations encourage the private sector to adopt the Common Rule. All right. It is not clear to me that we would need to go quite so far as to adopt all of the interpretations of DHHS of 45CFR46 such as this particular interpretation. So that would be a sort of more 10,000 foot kind of argument about being careful. I agree with Alex that I do not think this is the place to mount an opposition to the DHHS interpretation and I thought what we were trying to do here was to soft pedal that we think review is important, okay, locally and just reopens -- we are encouraging this kind of review as well by nonfederally funded.

DR. SHAPIRO: Jim?

DR. CHILDRESS: I have little to add to what Steve just said. I think that captures, as I understand it, the spirit of Bette's concerns and I would agree with those and I have some other reasons that were

connected with the kind of discussion we had yesterday about what gets brought into play if one brings in the whole apparatus of the research involving human subjects area. I think there are real problems in doing that in this area.

I prefer the soft pedalling approach to use Steve's language and I think in the text we can talk about the kinds of options here, the kinds of interpretations that have evolved, and leave it open for that. The principle of local review is an important one, I think. And I say I think because I am not as convinced as Harold is that it is necessary here.

If we look in recommendation eleven we are, in effect, setting up an assurance of compliance and I am not sure that enforcement mechanism is what is needed here given the role of the National Oversight and Review Panel, which again reads very different from what we would have in the ordinary -- if you go back to the human subjects model -- the ordinary human subjects model, okay, where you have the national body doing the kind of review that we are talking about. So I am not sure it is necessary but if it is necessary or at least appropriate I would prefer to see it stated as broadly as possible with the text talking about the kinds of

options and arguments involved and then see what happens.

DR. SHAPIRO: Alex?

MR. CAPRON: Do I understand that you are endorsing then a compromise in which the text would say, as it does here, local review. By "local" we mean institutional or -- I think we should not use the word "local." It is not like the City of Philadelphia is going to set up a review.

DR. SHAPIRO: I agree with that.

MR. CAPRON: The principle argument -- the principle argument it seems to me for using local review is the one that Steve reminded us of yesterday that some of the companies that have never done any human subject work may not have an IRB and it might be that HHS in implementing this would say that as an alternative to having an IRB it could have an embryonic stem cell review -- institutional review committee that would just do that and I think that -- in the text I would be comfortable with a commentary that said that it is now understood to be encompassed within the regs and not take a stand on that so to say for institutions that have IRB's the expectation is that they would cover it. It may be that institutions that do not could be covered

by specially crafted regulations and leave it at that. If that is what the compromise is I would vote for it.

DR. SHAPIRO: Well, as I am listening as carefully as I can to the commentary here, I think in my own mind the strongest argument for the IRB is it is known, its composition is known, the community knows how to access it and how to relate to it and so on. Those are very strong arguments. Laurie really was underlining those.

And talking just about my own idea of having a convened institutional -- some appropriately convened institutional review board, it does not have any of those things unless we start spelling them out and so on. And I think that is a strong argument, I think.

The other argument is also strong, unfortunately. Namely we want to keep at arm's length to the extent possible from the human subjects review and so I think our challenge is to craft a recommendation with commentary that reflects both of these points of view and it is all a question of what we want to say in the recommendation and what you balance that with in the commentary.

I guess on balance I think we ought to at the very least have the IRB's in the recommendation itself and perhaps try to look at alternatives in the

commentary such as what the private sector might use and so on even though in my own mind it is a close call.

Bette?

DR. KRAMER: Why can't we go the other way? When IRB's are intimately associated with the governance of human subject regulations?

DR. SHAPIRO: I understand that is the other argument and that is a good argument. That is why I say it is a close call. I mean, I do not have a killer argument against it.

DR. KRAMER: What about both? IRB's or other institutional --

DR. CHILDRESS: How about an appropriately constituted and convened local review body such as an IRB prior to consideration?

DR. HOLTZMAN: Well, I just -- in the second line "approved by an IRB or other appropriately..."

DR. SHAPIRO: Yes.

DR. FLYNN: But "appropriately" is not defined.

DR. HOLTZMAN: But I think that when you go into the text you will cite all the arguments you made about -- first off, you will cite the facts of the interpretations, all right, and then under current DHHS you have to if you are federally funded. All right. We

will then cite the prose that you said for the IRB's is a known entity, you will cite the other side of it that says that many of the issues that seem to be in play for an IRB about informed consent are not to the same extent in play here because you are dealing with a different kind of research --

MR. CAPRON: Steve, you have got all the issues of the donor and those are covered here under 46.206. You have to have the consent of the individual. They cannot be -- in other words, there is a lot here that is more relevant than you are suggesting.

DR. GREIDER: That is right.

DR. SHAPIRO: Diane, and then Rhetaugh?

DR. SCOTT-JONES: I would suggest that we say "by an IRB or other appropriately constituted and convened local institutional review body" to allow both of those to be there. I agree with Alex and with Laurie that there is already much that an IRB might have in place that would make them appropriate.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: I am not sure that we should add the option of another appropriate body. I do not think it is necessary becasue there are some institutions that might have more than one IRB. I think it is the concept

that we are trying to propose here and I would strongly argue that we keep the IRB in.

There was a statement on a previous iteration of this that said that regulations should be revised accordingly to take care of the recommendations that we have in here.

DR. GREIDER: I come down in favor of having both IRB and local review board because although I agree with the idea that there are -- IRB's already exist and we know what they are, as Steve pointed out, we are trying to encourage the privately funded sector to also voluntarily submit, and they might not have an IRB.

DR. DUMAS: They can establish one. There is no reason why they cannot establish one.

DR. GREIDER: That puts you under a whole different set of regs that we do not necessarily have to invoke here and so if you have both IRB and other appropriate review body I think it covers both of those areas.

DR. SHAPIRO: David?

DR. COX: I support that as a compromise position because I think that --

DR. SHAPIRO: Well, obviously if we -- I am going to ask in a moment how many commissioners would like the recommendation itself to read something like

"approved by an IRB other --" how many of you would like that? Obviously the commentary is going to be quite important here to look at both the strengths of the IRB review, the uncertainty of the connection between this and so on.

DR. DUMAS: May I ask one question before we vote?

DR. SHAPIRO: Yes.

DR. DUMAS: Is the intent of having the other local review body to provide this mechanism for the private sector? Is that the intent?

MR. CAPRON: To me it would be having an institutional --

DR. GREIDER: To some extent.

DR. FLYNN: I think it is more than that and that is why I am concerned about it.

(Simultaneous discussion.)

DR. SHAPIRO: It is more than that so that the University of Michigan, for instance, could --

DR. DUMAS: Have another body --

DR. SHAPIRO: -- constitute another body.

(Simultaneous discussion.)

MR. CAPRON: Not without a change in the present regulations they could not. I mean, I think part of what we are saying to HHS is maybe your

interpretation of that could be revisited and if you did you might say this is not a human subject thing, as Bette is saying, it ought to have a body constituted like an IRB specifically for this purpose, however, because most of what they are doing, I would agree with people, is not like what an IRB does when it is dealing with a living individual for whom consent is obtained, et cetera, et cetera.

DR. HOLTZMAN: I think it is useful to stop and say what are we thinking of as a case in our mind here and what would this panel be doing. All right. So take the case where the embryo is sitting in the bank, all right, and now someone is proposing a protocol to derive ES cells from it.

I think what this panel is largely doing is looking back and asking the question was the woman's consent to use the embryo in research, did it meet the following standards: No coercion, not paid, et cetera, et cetera. And I certainly agree with Alex there is that thing that is like human subjects research in terms of issues of consent -- the fundamental issues of consent.

Now people who know this stuff much better than I do, I do not know, but doesn't an IRB do something more than that when we are looking at a

protocol with human subjects? Right? It then looks at the actual protocol where there is an intervention of the subject and asks questions about safety, right, the value of the protocol relative to the safety or potential harm that the person is going to be subjected to, et cetera, et cetera, and to that extent there is an element of an evaluation of the scientific validity of the study because you cannot do the cost benefit or harm calculation without that.

None of that seems in play here, all right, in the same way. Are we asking the IRB to make the adjudication of such things as the culture conditions that Dr. Greider has provided for here are likely or not to generate an ES cell, therefore, all right, we do or do not think it is a good idea. That is where you start to get into it looks like a different kind of body at least from my perspective.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I think some of what Steve just said applies to any kind of research that an IRB might review. They are not always competent to review the science of it and in that case most IRB's call in a person to review it for that particular kind of research. So I do not think that is a compelling

argument in this instance. It is not unique to this. It would apply to all IRB work.

DR. SHAPIRO: Let me see what our options are in front of us. I think recommendation ten ought to specifically not the IRB as a minimum. The question is whether we -- option A, if I could describe it this way, will be a focus on the IRB. Recommendation ten having only the IRB. And then a commentary outlining other kinds of possibilities for people to think about. Maybe they read this recommendation and they might think through another possibility.

So one -- that is option A, which would have recommendation ten refer only to the IRB and then the commentary saying, you know, there are other alternatives. People who are really interested in this may want to pursue them and so on and so on but we do not have any recommendation. That would be option A.

Option B would be the one we have been just discussing, which would say something like "approved by an IRB or other " leaving the option open in the recommendation. And then a commentary following outlining the pluses and minuses of these various approaches.

It seems to me those are two things. So the IRB has got to be in there one way or another. But

option A would mention only the IRB and everything else in commentary. Okay. So let's just see how many of us prefer that option because if we do not go to option A, we will go to option B.

Laurie?

DR. FLYNN: I prefer that option.

DR. SHAPIRO: Okay. All right.

(Simultaneous discussion.)

DR. SHAPIRO: Now is everyone clear what I am asking? Okay. So let me see how many commissioners prefer option A, which is --

(A show of hands.)

DR. SHAPIRO: Okay. How many prefer option B?

(A show of hands.)

DR. SHAPIRO: Okay. Option B will be it. The commentary will contain the appropriate -- I will not try to summarize that again.

All right. Let's go on to recommendation eleven, which will obviously have to reflect -- I mean, really as it is stated here but obviously it will have to reflect what we have just decide so it might be something like "The Institutional Review Body..." rather than the local and so on "...described in recommendation ten should ensure compliance with any requirements

established by the panel, including confirming that institutions in the United States or abroad that supply embryos or fetuses have obtained them in accordance with the requirements established by the panel."

Bette?

DR. KRAMER: Do we mean fetuses or do we mean fetal tissue? I guess it does not matter.

DR. COX: You do not want to go there, Bette.

DR. KRAMER: No? Okay.

DR. SHAPIRO: David, what is your --

DR. COX: Because if the fetus -- if it is fetal tissue and embryos, okay, then embryos are living.

DR. KRAMER: If it is -- say what? If it is what?

DR. COX: If it is embryos or fetal tissue then it is fetal tissue but not embryo tissue.

DR. KRAMER: I think what I am confused about is does -- do the words "embryos or fetuses" relate to the two different known techniques of deriving the cells?

DR. SHAPIRO: Known sources.

DR. KRAMER: Known sources. Right.

DR. SHAPIRO: Yes.

DR. KRAMER: But is the source called "fetus" or is it called "fetal tissue?"

DR. SHAPIRO: Cadaveric fetal tissue is what we have been using, I guess, in a lot of these.

DR. KRAMER: Right. But shouldn't that --

(Simultaneous discussion.)

DR. KRAMER: -- shouldn't this correspond to that?

DR. SHAPIRO: You are right about that.

DR. DUMAS: Are we arriving at different approaches for the review for this type of tissue than for other tissue than we put in our other report? The use of human --

DR. SHAPIRO: Oh, yes.

DR. DUMAS: -- tissue.

DR. SHAPIRO: We certainly are.

Thank you very much for that. Excuse me but I just want to make sure I get this written in.

DR. HOLTZMAN: Can we change institutions to individuals and organizations?

DR. SHAPIRO: To --

DR. HOLTZMAN: On the third line.

DR. SHAPIRO: Yes. You want to change "institutions" to "individuals."

DR. HOLTZMAN: Or other organizations.

DR. GREIDER: May I just note that in rewriting all of the commentary that is going to go in chapter ten it may be that -- I mean, in recommendation ten, it may be that recommendation eleven would actually be part of recommendation ten. I hate to bring this back up again but I will just leave it to the staff. It does not necessarily follow to me that there have to be depending on what the commentary says.

DR. SHAPIRO: I agree.

Okay. We will now go to recommendation twelve. "When reviewing research protocols using embryonic stem cells and embryonic germ cells all federal agencies should ensure that their review processes comply with any requirements established by the National Oversight and Review Panel (see recommendation eight) paying particular attention to the adequacy of the justification for using such cell lines."

This is, I think, unchanged from the previous one.

Okay. Let's go on to recommendation thirteen. "For privately funded research on ES/EG cells that would otherwise be eligible for federal funding NBAC encourages researchers and sponsors voluntarily to adopt the recommendations of this report that apply to

such research." It should be a period after that. "This includes submitting protocols to the National Oversight and Review Panel for the derivation of embryonic stem cells and embryonic germ cells for review and for the certification of cell lines."

MR. CAPRON: "Such cell lines."

DR. SHAPIRO: Okay.

Recommendation fourteen: "For research projects that involve deriving --" Yes?

DR. HOLTZMAN: Is the "for" phrase --

DR. SHAPIRO: Yes.

DR. HOLTZMAN: -- there in the wrong place? Move the "National Oversight and Review Panel" to after the word "cells" in the fourth line.

DR. SHAPIRO: Right.

DR. HOLTZMAN: This includes submitting protocols for the derivation of --

DR. SHAPIRO: That is right. Thank you very much. Anything else on that one?

DR. HOLTZMAN: Sorry.

DR. SHAPIRO: No, that is entirely --

(Simultaneous discussion.)

DR. SHAPIRO: Fourteen: "For research projects that involve deriving ES/EG ells that would not

be eligible for federal funding under recommendations three and four in this report NBAC recommends that:

"(a) professional societies and trade associations develop and promulgate ethical safeguards and standards consistent with the principles underlying this report;

(b) privately funded researchers conducting this research and their sponsors should voluntarily comply with these safeguards and standards."

MR. CAPRON: We left out the phrase "privately funded" at the beginning.

(Simultaneous discussion.)

MR. CAPRON: Or is it not necessary to say that? I do not know.

MR. CAPRON: Maybe we do not need this.

DR. DUMAS: It is not necessary.

DR. SHAPIRO: Let's see what we have in the previous one.

MR. CAPRON: The previous one says "privately funded" because it just did not make sense to say "otherwise -- that would otherwise be eligible."

DR. SHAPIRO: Carol?

DR. GREIDER: In both recommendations thirteen and fourteen we are basically referring to research embryos.

DR. SHAPIRO: Not in thirteen.

MR. CAPRON: No, thirteen is the --

DR. GREIDER: I am sorry. Fourteen.

DR. SHAPIRO: That is right.

MR. CAPRON: That is right.

(Simultaneous discussion.)

DR. SHAPIRO: Recommendation three and four refer to research embryos.

DR. GREIDER: So should we just say that rather than referring back to recommendations three and four, you know, the not eligible for federal funding under recommendation three and four. Can't you just say research embryos?

DR. HOLTZMAN: The discussion over lunch yesterday, which we generated this, wrestled with the following problem: There is virtue in the clarity in thirteen of saying research involving -- privately sponsored involving excess or spare embryos and in fourteen saying for research involving research purpose embryos.

Alex made the argument that what is subject -- what is and is not available for funding may change over time and that, therefore, we wanted to keep it more generic.

I personally, having slept on it overnight, would advocate in trying to address Alex's issue about making the recommendations clearer because I find myself again thinking about the people who read these things only reading the bolded text, all right, and having to leave to them to infer that recs three and four are research purpose embryos.

So I -- it says the same thing. The question is how --

(Simultaneous discussion.)

DR. HOLTZMAN: -- communication function. Is that a fair statement of the argument, Alex, or the thought process?

MR. CAPRON: Right. And three and four used to have the language which we have cut out throughout all of this, "at this time" on the basis that everything is "at this time."

DR. DUMAS: At this time, right.

DR. HOLTZMAN: Yes.

MR. CAPRON: But that is the basis that at some point under three and four we recognize the possibility that the national body would recommend and HHS would accept or Congress would accept other --

DR. GREIDER: I understand.

MR. CAPRON: And I do not think within bolded text -- I mean, a cross reference to another recommendation in the same chapter or if these recommendations are printed in some point in the report just as recommendations without commentary is not hard to cross reference.

DR. HANNA: I would just suggest that you do try and find some way of clarifying it because the phrase "that would otherwise be eligible for federal funding" can mean all kinds of things. It can mean that they did not complete their budget form on their R01 sheet properly or they did not -- you know, there are a whole lot of reasons why something would not be eligible for federal funding.

MR. CAPRON: That was why, Kathi, we put the phrase "not eligible" under recommendations three and four, precisely because that argument was also raised that, you know --

DR. DUMAS: But what is the objection to just spelling it out?

MR. CAPRON: Then you just lock yourself in. Under recommendation --

(Simultaneous discussion.)

MR. CAPRON: -- embryos created for research purposes --

(Simultaneous discussion.)

MR. CAPRON: -- conversely saying would not be eligible because they involve embryos created for research purposes, see recommendation number four.

DR. SHAPIRO: That actually is clearer.

(Simultaneous discussion.)

DR. DUMAS: What you are really saying is that for research protocols to develop embryos for research purposes, right, that is what fourteen refers to, then I think it ought to be said. And I do not think that that locks us in any more than any other recommendations.

DR. COX: Recommendations three and four are locking us in anyway and so --

DR. DUMAS: That is right. So why should somebody have to go all the way back to three and four?

DR. SHAPIRO: If you say the following: "For privately funded research projects that involve deriving ES --" excuse me. "Involving deriving ES/EG cells from embryos created solely for research purposes and that would not be eligible for federal funding under recommendations three and four in this report NBAC recommendations that..."

DR. HOLTZMAN: Yes, that is great.

DR. GREIDER: That is clear but I do not think EG belongs in there.

DR. HOLTZMAN: EG should be deleted.

DR. SHAPIRO: That is correct. Excuse me. That is right.

DR. HOLTZMAN: And then could we make the commensurate change in thirteen to make clear what we are referring to, spare embryos? They would be eligible because they are from spare embryos or cadaveric fetal tissue.

DR. SHAPIRO: Okay. We will make that parallel.

Yes, Alex?

MR. CAPRON: Is the "because" clause there?

DR. HOLTZMAN: I am not trying to wordsmith it but I think --

MR. CAPRON: No, I mean, my concern is they are not eligible because they involve that as it were. It is --

(Simultaneous discussion.)

MR. CAPRON: They are eligible to that extent, I mean, an then we get into the reverse of the point Kathi made, which is they are eligible if they involve that and if they meet a whole bunch of other --

DR. COX: That is exactly the point that we want to make so in that situation you do not want to just have it be that because they are spare embryos that is a necessary but not sufficient category.

DR. HANNA: Spare embryos and/or --

DR. COX: But they are also --

(Simultaneous discussion.)

DR. COX: That includes everything. It is required.

MR. CAPRON: On this one, Steve, I actually think the economy of just saying would otherwise be eligible for federal funding is sufficient.

DR. DUMAS: Are you talking about recommendation fourteen now?

DR. SHAPIRO: Thirteen.

DR. DUMAS: Thirteen.

MR. CAPRON: That one then covers the situation in the future if other categories of ES/EG cells are now permitted and eligible for federal funding.

DR. SHAPIRO: Okay. We will work out the language on these two. I think we understand what we want to say here. It has been helpful to clarify.

Recommendation fifteen I have not even looked at and it looks to me like it has the words in it I did not like before.

(Simultaneous discussion.)

DR. COX: One thing, Harold, the word "otherwise" should not be there. It is eligible for federal funding. It happens to be privately funded. So --

DR. SHAPIRO: Where is this?

DR. COX: Recommendation fifteen. "For privately funded research on ES/EG cells..." and it could be both "...that would be eligible for private funding."

DR. SHAPIRO: It actually reads better that way.

MR. CAPRON: Actually much better that way, David.

DR. SHAPIRO: All right. So I apologize. We are going to -- I do not have anything to say about fifteen but I have to say I do not like the word "sunset" but let's see what the comments are.

Diane?

DR. SCOTT-JONES: I would suggest breaking the idea into two sentences and say something like the National Oversight and Review Panel and the public

registry described in recommendations eight and nine should be discontinued after five years, period. The DHHS Secretary should arrange an independent evaluation of the process and substance of their activities to determine whether these mechanisms have adequately fulfilled their functions and to determine whether they should be continued to be established.

DR. SHAPIRO: I have a different kind of suggestion and see how you like that, which would be a shorter suggestion, I think, in my mind accomplishes it all and most of all gets rid of the "sunset" clause.

The National Oversight and Review Panel and public registry described in recommendations eight and nine should after a period of five years be independently evaluated. We do not have to sunset it ourselves. It can be independently evaluated and people can make whatever decisions they want.

DR. SCOTT-JONES: That is fine.

MR. CAPRON: The sunset idea is a little bit hold the feet -- everybody's feet to the -- be serious that you have to have reached a positive -- but which is -- but we do not have to use the first phrase. What if we said, "Should be chartered for a fixed period of time such as five years?" At the end of that period or before the end of that period the process and substance

of the activity should be independently evaluated to determine whether they adequately fulfilled and should be continued.

DR. SHAPIRO: Well, that goes into two sentences which is the structure that Diane suggested.

MR. CAPRON: Yes. I agree with Diane.

DR. SHAPIRO: Okay. Let's see what we can do.

DR. SCOTT-JONES: I would also put it in the active voice to say who should arrange the independent evaluation.

MR. CAPRON: Yes.

DR. SHAPIRO: Okay. So we agree on fifteen that we will replace it with two sentences. One is it establishes a fixed term like five years for this and the second of which talks about the evaluation and we will get DHHS to -- that is what I would suggest anyway.

DR. DUMAS: Yes. I would, too.

DR. SHAPIRO: Do the evaluation -- you know, decide what kind of evaluation to do and so on. Using this language about the mechanism. Okay.

Well, let me make the following suggestion as we draw this part of our discussions to a close. We will get a new set of recommendations incorporating these final changes to everyone, not tomorrow but

certainly no later than the next -- than the day after tomorrow, which will be Friday.

If there are any remaining concerns please let us know immediately because otherwise we will assume this is a set of recommendations around which we are going to build our executive summary and then the report. And I want to repeat what I said before. We have a lot of rewriting to do in response to many of the good suggestions that have come up.

If there are additional suggestions, marked up copies, anything like that to help us take -- get the benefit of your own thoughts, ideas and perspectives, it would be extremely helpful. We are going to be writing this more or less nonstop from tomorrow morning on. So the sooner we hear from you the better. We are very dependent on your quick feedback here.

Diane?

DR. SCOTT-JONES: I have two more comments that I can make now. They are very brief.

DR. SHAPIRO: If brief, yes, becasue I wanted to get a chance to get the international group started.

DR. SCOTT-JONES: For recommendation twelve, consistent with other changes that we have made. I would start this sentence with "all federal agencies

should ensure that their review processes for research protocols using embryonic stem cells and embryonic germ cells comply," and then the rest of it will be the same. It is just consistent with other changes that we have made to put all federal agencies should ensure.

DR. SHAPIRO: Have you written that in?

DR. SCOTT-JONES: Yes.

DR. SHAPIRO: Okay. That is very helpful. Can you just give it -- pass it up here when you are through?

What is the second one?

DR. SCOTT-JONES: And then the other one is for recommendation five. I would like the commentary still to say something more about the importance of discussing sources of funding in commercial interest because we changed that to soften it somewhat to say if known after the bullet one, two, three, four, that refers to funding and commercial benefits.

MR. CAPRON: What is your concern?

DR. SCOTT-JONES: Just to make sure that in the text there is some reference to the importance of discussing that because it was brought up that in many instances that would not be known at the time the request is made to the potential donor.

DR. SHAPIRO: Okay.

MR. CAPRON: This is a general comment on the report and I think the report will read much better if we do two things. If we avoid the use of the word "we" except when we mean the commission. In other words, the "we" that is in general writing just because it is confusing. And that if we avoid saying "NBAC" this and "NBAC" that to the extent possible.

DR. SHAPIRO: I agree with especially the latter.

MR. CAPRON: It just -- you know, in our report to speak of ourselves in the third person is --

DR. SHAPIRO: I agree with that.

Diane?

DR. SCOTT-JONES: And there is also places where we say "NBAC did X" and then we refer to NBAC as it.

MR. CAPRON: Yes.

DR. SCOTT-JONES: Those are really terrible.

MR. CAPRON: It is just odd.

DR. SHAPIRO: Okay. Other kinds of editorial suggestions? We are anxious for -- please, if you want us to pay any attention, write them down. We just cannot keep track of all these suggestions that are not written down. So everybody has a writing request and homework assignment.

Now remember, I am going to repeat it, this is the third time this morning, any marked up copies, please leave them. One, it will save you the trouble of carrying it all the way back. Second, we would just greatly benefit from it.

DR. COX: Can we e-mail marked up copies? Can we e-mail corrections of these, through e-mail?

DR. SHAPIRO: E-mail is great. Hopefully, tomorrow.

DR. COX: Yes, exactly. To who?

DR. SHAPIRO: Everyone. You can -- anything you like. To everyone is best so that everyone gets a chance to look and comment. If that is not possible just send it directly to Eric or myself.

Yes, Bette?

DR. KRAMER: Harold, what are you thinking about for the completion of the text? When do you think we might have a --

DR. SHAPIRO: I do not want to make a specific forecast but we are going to try to do it in the next couple of weeks. We are not waiting months here. So you will have to be -- I mean, really we need all your comments by the beginning of the week. After that it is almost too late for us to accomplish the writing.

Why don't you introduce the next section?

THE INTERNATIONAL PROJECT

DISCUSSION OF DRAFT OUTLINE FOR THE INTERNATIONAL PROJECT

DR. MESLIN: Thanks very much for everyone's patience. We had originally scheduled a discussion of our international project for earlier today but as you all know we have been working on the ethical use project.

Dr. Ruth Macklin, who has joined the NBAC staff as a consultant on a part-time basis over the summer has been working with us to flush out a working outline of the International Project. Many of the consultants to the commission on the International Project are here with us today in the audience.

I would also like to let the commissioners know that we have a new staff member that has also joined us for the summer, Alice Page, who is here. Alice may just want to stand up and say hello. You will meet her more, I hope, in the months to come.

I thought with the time that we have available to us, the half an hour, that Ruth would be able to at least introduce and discuss the draft outline, which is contained in your briefing books. It is actually the last item in your briefing books. That

both Ruth and Alex, as necessary, could lead some discussion and get some input.

DR. MACKLIN: Thank you. I guess we are going from the micro to the global. This is a very tentative outline and it is an outline that I developed with Eric's help and some comments from Alice Page for the international report.

I am not sure how much all the commissioners know about the empirical studies that are -- so you know that there are ongoing empirical studies that are referred to at various points in this outline and will form part of the data that will -- for flushing out the report so I have got this in the introduction and five chapters, I believe, six chapters.

The introduction, of course, will explain why this report is needed, briefly describing some of the key events and circumstances that lead up to the -- that have led up to the need at this particular time for the report, and as everyone here knows because they were previously here when I spoke once before, in Cleveland, I think it was, on the international issues.

There were, I think, a few seminal events. Namely the controversy that erupted over the placebo controlled AZT maternal to child transmission studies. That controversy died a natural death, although the

issues that it raised have not gone away and, in fact, are ongoing and if we look towards the future are likely to emerge again with the vaccine trials, HIV vaccine trials, many of which will be supported by the U.S. and other international agencies and, of course, conducted in some of the resource poor countries.

The introduction will simply also list and briefly describe other efforts going on simultaneously to look at the international collaborative issues so although it is certainly a concern in the United States, in part, flowing from that AZT controversy but also because of the work of the -- the support of the NIH in future studies. Other countries are experiencing the same problems or addressing the same dilemmas.

Now the outline below, following the introduction, simply lists by chapter what the ingredients or the elements will be in each chapter. If this does not make sense as the report begins to get written and as the data is being analyzed, as data are being analyzed then we will, of course, change the order.

Chapter one should give a historical perspective on U.S. sponsored research in other countries and particularly highlighting some of the problems, complaints, difficulties that have arisen.

There is a lot of anecdotal information around and a lot of people cite problems that have arisen in the past, issues of exploitation and other concerns.

I think we need to do it a little more systematically and raise the question, as the last second brief paragraph says, the point of the chapter will be to determine whether any of these past alleged abuses might still occur today or whether current U.S. Federal requirements adequately protect research subjects in other countries.

I refer to -- I have used the word "anecdotal." Perhaps I ought also say refer to journalistic accounts. We frequently read every time a journalist writes in the Washington Post or in the New York Times we see an account of some current problem or alleged problem, and there is always a response either from the researchers themselves or from the sponsors of the research that never gets published but becomes known to any of us who happen to hear their responses.

And these responses are often attempts to explain, justify and correct the misstatements if there were misstatements in the press. So that is one of the reasons I think we need a little bit better research to document things and go beyond -- if we can, go beyond

the journalistic allegations. The hope is that we get outside research preferably by a trained historian.

Chapter two will focus on applying the U.S. research regulations in other countries and these -- the specific content will be problems encountered by researchers. Now there are there ongoing studies. Jeremy Sugarman's, Nancy Kass' and Adnan Hyder, and there may be additional illustrations but all of these will look -- are seeking to -- through interviews, case studies and focus groups, these empirical studies are designed to find out both from U.S. researchers who are doing research in international settings and from researchers in the countries where the research is being done, who are collaborating with the U.S. research.

So any other information in addition to those empirical studies that is relevant will be brought in there and again the point of the chapter will be to see which and how many barriers stem from difficulties in applying the U.S. regulations in other settings and which problems stem from factors that have little or nothing to do with U.S. regulations.

Eric Meslin asked me what is an example of that, problems that have little or nothing to do with U.S. regulations, and I actually could not think of one but I know they must be out there because certainly not

all problems are going to come from applying the U.S. regulations so that will be another and that, of course, should inform the report. After all, if there are problems that arise in international collaborative research that cannot be traced to the regulations there might be other remedies but the remedy would not be to seek any changes or expansion or modification of the U.S. regulations.

Nevertheless, I know, again anecdotally but not systematically, that researchers complain all the time about how the U.S. regulations constrain them in doing research in other countries and, in fact, I have been in touch with at least one person and colleagues at NIAID that sponsors the AIDS research and he said he would be delighted to speak with me and, you know, perhaps others to -- might even want to come and speak before the NBAC to outline some of those problems. I mean, since AIDS is on the front burner, the controversy over the AZT was an AIDS controversy, the vaccine trials are also AIDS, so I think looking at some of those might be instructive.

MR. CAPRON: I had thought from some of the discussions that we intended to include in the category at the end of that sentence that had little or nothing to do with U.S. regulations situations where most

countries could easily comply. For example, in the make up of an IRB. But a particular country because its experts happen to be few and far between or are in different cities and actually simply going from city A to city B is a big deal and something they do not do frequently that it is difficult to carry out some of the functions the IRB is supposed to be doing.

And one could say that that stems from the regulation but it is not really something about the regulation to which anybody objects in principle. It is simply that --

DR. MACKLIN: Practical barriers, yes.

MR. CAPRON: -- practical barriers and I thought we were going to use that as the kind of illustration but maybe I misunderstood you.

DR. MACKLIN: No. I think that is a good example of one and --

MR. CAPRON: We heard about such problems in Nigeria or other cities.

DR. MACKLIN: Right. And, in fact, efforts are going forward. Probably -- to my knowledge, not by people in the United States but that may be my ignorance but certainly at the international level through the Joint United Nations Program on AIDS and the World Health Organization to do capacity building and one

feature of capacity building is specifically to increase the numbers, the knowledge, and the numbers of people who are able to do ethical review and, thereby, serve on -- we are the only country that calls these things IRB's by the way. And I think in a way we have to be careful. We have to use that word because that is our word in this country but they call them usually Ethical Committees or Ethical Review Committees or Research Ethics Committees, one of those terms.

So that is a good illustration. Thanks, Alex.

The -- I am sorry, sure. Yes? Sure.

DR. SCOTT-JONES: I have just a really brief question. I am very interested in the empirical work of Jerry Sugarman and Nancy Kass. They talked to us briefly in a previous meeting and I was wondering if we could get an abstract that would lay out the design of their studies and I also wondered are those -- about the funding. Does NIH fund those studies or do we, NBAC, fund them?

DR. MESLIN: We fund them. That is part of our contract with them. Jeremy and Nancy are both here if you would like to ask them a question. They -- either or both. Nancy or Jeremy, do you want to just respond?

DR. SCOTT-JONES: Just to get an abstract of the --

DR. MESLIN: We have given you a summary but we can give you a more updated one if you would like. We also have --

(Simultaneous discussion.)

DR. SCOTT-JONES: That would be great.

DR. MESLIN: Happy to do that. And, yes, NBAC funds this but it also goes through institutional review at all the relevant places as well as clearances that are required at various places, yes.

DR. MACKLIN: So you will provide that then.

DR. MESLIN: Yes.

DR. MACKLIN: Okay. Let me go on to chapter three, which is a timely coincidence because Patty Marshall just walked into the room and this chapter will be drawing on her largely but on her research and possibly more.

The third chapter will address problems and concerns in applying the U.S. research regulations in other countries once again but this time barriers stemming from cultural and religious differences and this is often stated -- again another anecdote, people from other countries say, "We cannot apply your

regulations." It almost always comes down to variations on informed consent.

It would be very interesting to see something other than informed consent in this category but I mean there are aspects of informed consent. To give an example, permission that might be needed from a male member of the household for a woman to enter research. That is related to informed consent. It is not the consent per se but it is certainly related to it.

I would like to sort of be able to draw on some other examples if we can but here Patty Marshall's project which, as I understand it, is focusing largely on informed consent although other things may bubble up will be really the center piece.

And so noted here in the first paragraph at the end since Marshall's study focuses on informed consent, additional research will be needed to identify areas beyond consent that give rise to cultural, religious or political barriers.

Now political is stuck in there again at the excellent suggestion of Eric Meslin but I think we need a different kind of analysis here and I remain uncertain whether political belongs in the same chapter under the same heading so we welcome suggestions or observations

because cultural and religious is one thing and political can be anything in any country.

So again the point of the chapter is to determine whether U.S. research regulations may justifiably be broadened or made more flexible to accommodate some cultural differences without lowering substantive ethical standards embodied in U.S. regulations. And, of course, this requires some assessment of whether changes in the regulation would succeed in avoiding these problems. So I think focusing again on informed consent -- I mean, if you think about it, that would be where that would lie. The note just simply again reiterates the problem with the political factors.

Chapter four will undertake to compare key elements in U.S. regulations and regulations in other countries in order to identify key elements on which U.S. regulations differ from or conflict with those in other countries.

Now since this international report will be largely on collaboration or international research sponsored by the U.S. in what are called developing or, a term that will probably soon be abandoned, or resource poor countries. Nevertheless there are collaborations with other industrialized countries and some of the U.S.

sponsored research and international collaboration takes place with industrialized and, in fact, Jeremy's project, I think, deals with at least one, if not a couple of industrialized countries.

The industrialized countries are the ones that are the most likely to have an elaborate set of research regulations similar to those that we have. Less likely but happening in other countries. I know in India the MRC, Medical Research Council, in India has just promulgated a set of research regulations so things are quickly developing in the other countries, the so-called developing countries, and this will really, I think, undertake -- we need to undertake a fairly detailed comparison but, of course, we cannot compare everything in the world.

So what I suggest here is that examples should probably begin with the countries represented in the studies by Sugarman, Kass, Hyder and Marshall at least to be able to connect and make this report systematic. That is not only are we going to look at the regulations, not only are we going to investigate the researchers but we will have a total picture or as total as you can get without being complete of these individual sites.

One other -- others might be chosen and one other possible criterion would be countries in which the NIH and the CDC, in particular, have conducted a substantial amount of collaborative research. So the next is a list -- I do not want to go through this list now because it is almost self-evident but again we welcome additions to this list or clarifications if needed of the elements that would be compared. Okay. It includes one through four but is not limited to one through four. Some may not be so important for our purposes.

I mean, number four, I am not sure whether the presence or absence of special rules for children, prisoners, fetuses, mentally impaired individuals and pregnant women, whether that is as relevant to the concerns of this report. It may be but perhaps it may not be.

Now, also, this is, as you can see, the longest -- there is no symmetry here in this. The paragraph in the middle of the page says the chapter will have to specify procedures to be followed when the U.S. and the collaborating countries, IRB's or research ethics committees fail to agree in approving or -- it should be approving or disapproving a research protocol

-- or disagreeing about specific provisions of the research.

Our federal regulations are totally silent. They say nothing about -- they do not even say anything about multisite trials in this country and what happens when different IRB's look at it. So this may be a broader problem that applies as much in the U.S. as elsewhere. But I do believe -- I have here "may" -- some countries' regulations may address this point.

I attended one meeting in which someone from the U.K. said that the MRC research regulations require that both IRB's in the sponsoring country and of the host country both approve and that they agree on all the elements before the research can go forward.

And yet there are -- I know again from one anecdote there has been a point of contention on that. Some people in the resource poor countries say, "It is taking place in our country, we should decide. We do not want some big gorilla telling us what do. Well, we know our people. We know our culture. We know the burdens o disease. And, therefore, we should be the ones to have the final or the ultimate authority in case of any disagreement." So that is something that should be addressed.

Again, the point of the chapter, to determine where there are gaps, inconsistencies and conflicts between -- it should read -- between U.S. regulations and those of -- well, there could be gaps in U.S. regulations and conflicts between U.S. regulations and those in other countries.

Alice Page asked whether there is something like a regulatory history that can explain differences and discrepancies, and the report will have to draw some conclusions regarding what to do about any such discrepancies where they may exist in proposed collaborative research, and here are some alternatives.

Yes, please.

DR. SCOTT-JONES: I have a question about whether in this chapter or perhaps in another one you would address the issue of in this country the fact that research that is carried on without federal funding is not subject to the same rules and how does that affect the comparison of the U.S. to other countries?

DR. MACKLIN: Do you mean whether, for example, research that is conducted in other countries by -- let's say by a pharmaceutical industry exclusively without any contribution from U.S. federal funds, whether that would be -- whether that would be the

analogous situation that exists in this country. I mean, I am not sure.

DR. SCOTT-JONES: Well, I think there would be a lot of implications for comparing the U.S. to other countries when you talk about U.S. regulations because U.S. regulations do not apply to all U.S. researchers.

DR. MACKLIN: Right, that is true. Well, we will have to consider what to do about that. Interestingly enough, all other -- most, let me say most. To my knowledge, most other countries when they have research regulations they apply to everything that goes on in the country. They have a Ministry of Health. We do not have a Ministry of Health. They have a Minister of Health. And all of the -- most of the regulations in those countries come out of a Ministry of Health and they apply to all research that is conducted in the country, whether it is sponsored locally, whether it is sponsored -- conducted and sponsored locally, whether there are outside sponsors.

DR. SCOTT-JONES: I think throughout there is sort of a theme that the U.S. regulations might be at a higher standard somehow, that is sort of implicit in the way you are approaching this, and it may be that -- what you just said, that other countries have a more uniform application of the regulations that they do

have. That might be something for us to think about or have addressed in your report.

DR. MACKLIN: Yes.

DR. HOLTZMAN: I think this is a fascinating area and I think it is important to remember that the overwhelming majority of human subjects research conducted by the pharmaceutical and biotechnology industry is in support of drug registrations, which is controlled by the FDA and under FDA regulation you are essentially coming under the purview of the Common Rule. Okay.

But it does raise the further question of the focus of this report on research sponsored by whom because I saw you talking to someone last night who has responsibility for a multi-hundred million dollar worldwide registration effort on behalf of a major pharmaceutical company and in the current economic environment all drugs are being developed through simultaneous worldwide registration and the industry runs into all sorts of issues about how do I do the same study in the U.S. versus other countries.

And I think our empirical studies focusing on research that is under the CDC and NIH when, in fact, there may be a ton more research going on by the pharmaceutical industries worldwide where we could get a

heck of a lot of information about the issues and problems. And they range -- you know, they range from the U.S. requiring studies, for example, of placebo controls by the FDA, which are considered immoral in other countries, certain other countries.

So when you say "stringent," stringent cuts more than one way here. So I just think it would be --

DR. MACKLIN: Indeed, and we will come to some of those points, Steve, on the very next page. Okay. Because we are -- there are some things that -- international guidelines that address it.

I have at the bottom of this page here research is needed to address the following questions: Have there been any actual conflicts stemming from these discrepancies? I mean, it is one thing to identify discrepancies that exist between U.S. regulations and others but they may never have posed any conflict. There is just a discrepancy.

If so, who has done that? That is who has been the adjudicator or the one to resolve the problems? What agency? Is it the FDA when it is under its jurisdiction or the CDC, et cetera? So again this has to look at -- again a recent history, not back too far but recent history just to see whether any such conflicts have arisen.

Now chapter five gets to some of the questions that Steve had just made. This is a comparison of U.S. regulations and current international ethical guidelines of which there are several. And just as a reminder, the -- one of the arguments that was given by the severest critics of the placebo controlled AZT mother to child transmission studies.

Those arguments were based on clauses and provisions in the declaration of Helsinki, which I do not believe anybody in the United States ever looks at even if they know about it, and another much elaborated version that is much more detailed, the CIOMS, Council of International Organizations of Medical Sciences, which really does not mean anything. The CIOMS guidelines -- well, I mean, it is not really a council and it is not the organizations but it is the -- it is a body that is a private body, nongovernmental body loosely connected with the World Health Organization.

And those guidelines, the CIOMS guidelines, rest on the Declaration of Helsinki. They do not conflict with it but they elaborate in much greater detail and say a lot about international collaborative research.

I do not know of any examples other than the controversy that arose over the AZT where there has been

an invocation of those international guidelines by people looking at U.S. sponsored research.

MR. CAPRON: They are certainly invoked in many of the countries as their guiding principles.

DR. MACKLIN: Yes. I meant in this country. They are, indeed, in other countries and especially in countries that have not had to date or still do not have any regulations or any code of federal regulations or rules. They are the guiding principles used by researchers. I know that when WHO in some of its programs sends out the application packets for researchers they include the Declaration of Helsinki and the letters that come back that are signed by people attesting to their plan to conduct ethical research saying we are going to follow the Declaration of Helsinki. So that is certainly true.

Now there is one other -- I have one other document here and it refers -- it relates to what Steve was talking about. It is the ICH. I have not spelled that out here and I have even forgotten what it stands for. It is the International Conference on Harmonization. And it deals with drugs and drug research only.

And the International Conference or whatever the "C" stands for is essentially an international -- I

do not think it is a treaty but it is an international -- it is a document that was supported by and agreed to by the United States and European Union and Japan. Okay. All industrialized countries and the key point there is the harmonization, namely to have harmonization and it is very detailed. It incorporates very much of what is in the U.S. federal regulations and more.

So this kind of comparison -- I mean, that is a document which in the pharmaceutical -- in industry sponsored research must be adhered to, I take it, because that is the -- if it is drug development.

DR. HOLTZMAN: Right. The idea is that by harmonizing the regulations both with respect to consent to what is a valid study but also what will be considered a valid study supporting safety and efficacy that you would then be able to reference data from a study undertaken in one country with another such that economically it makes sense because you do not have to replicate studies and from the human subjects protection perspective you do not have to replicate studies as well.

DR. MACKLIN: And there are a lot of procedural rules there too about research ethics committees, their compensation, et cetera.

I will leave to your silent reading that middle paragraph there because that is one of the key elements that is omitted from U.S. federal regulations that is causing much of the problems in international research but let me just race up to chapter six, which is the summaries and recommendations.

It is sort of obvious at least the following items should be addressed. In international collaborative research what are the obligations of U.S. sponsors when international guidelines include requirements that are not included or even mentioned in U.S. regulations. I mean, this is almost the other side of the coin. One question is what happens when we have rules that other countries do not have or do not want to follow.

This is what happens when you have got provisions in international documents and declarations that other countries adhere to or rely on and they see the United States not complying because it is not in our regulations.

Now I put "higher standard" in quotation marks because we, of course, are going to have a debate about what standard are the higher and what higher means and what are the criteria for higher. So whether the

higher or more detailed requirements should be adhered to, those are the questions under (a).

Under (b), how should the collaboration between sponsor and host country proceed? I mean, this is largely procedural but can be very important. The committee that I chair, the Ethical Review Committee at UNAIDS, the Joint United Nations Program on AIDS, and we had a huge debate on the committee about a seemingly unimportant trivial matter, namely the UNAIDS Ethical Review Committee must approve the research protocol and the UNAIDS regulations or our guidelines require local ethical review. The point that Alex was referring to before. Now assuming that there is local ethical review and they can put together a body to do it, which should go first.

Well, I mean, there was a fierce debate but it really did touch on questions of power, empowerment, rubber stamping, and all the things that you can think a discussion like that might raise. So that is procedural but held by some people to be very important.

What about disagreements when they arise between U.S. researchers or the sponsoring agency and local researchers in a collaborative trial or between the host country, IRB, and the sponsoring country IRB? I mean, what to do about disagreements.

And (c), what level of care and treatment should be provided to participants in clinical trials? And the questions that follow relate both to the controversy that led to some of this -- to the need for this, namely the AZT trials, also the just beginning and future HIV vaccine trials? What level of care and treatment is it? What is normally available in the sponsoring country? What is available in the host country, et cetera? Again this is a point on which U.S. regulations are totally silent. They say nothing about treatment of any research subjects within the United States. I mean, forget abroad. Nothing about that.

And (d), at the end of the trial what must be made -- what, if anything, must be made available? The CIOMS guidelines state that successful products that emerge from research, international research, must be made reasonably available. Okay. They do not say by whom and they do not say to whom, and people have argued on both sides of this.

And then finally some questions about global justice. What does global justice require?

So I am sorry to take so long in going through the outline but I wanted to give a kind of rich picture of where it should go and I guess there is much more to be said.

DR. SHAPIRO: Thank you.

Alex, do you want to make a comment?

MR. CAPRON: The only comment I would have is to remind people of the note on page one, which Ruth alluded to. It may well turn out, and I frankly have a small personal preference, that we make this report turn around some substantive issues of content and that we -- in terms of the differences and the problems that actually have arisen, that there is certain generic categories, and that we avoid the kind of process in which we have historical reviews and then summaries of some research and summary, rather than taking the research and the history and applying them to a particular problem.

As Ruth says, that is pretty much going to be determined by what the sort of total data bank looks like at the point where she and the staff are trying to write this and it may turn out that the organization, which is excellent, the organization which is here, does work the best if certain substantive problems have sort of left out. Our main concern here is not an abstract dissertation about collaborative research and so forth. It is are there needed changes in HHS or FDA regulations to take account of international concerns and the concerns of the host country.

Is that fair?

DR. MACKLIN: Sure. I think one very direct way of doing that would be -- one area would be informed consent. Another would be risk benefit and differences in risk benefit in different countries. A third would be the areas not addressed by the United States regulations such as the care and treatment issues.

MR. CAPRON: Right. And I am just saying that it might turn out that focusing it that way makes a crisper presentation leading us more quickly to --

DR. SHAPIRO: Alta?

MS. CHARO: I hope this will not be considered inconsistent with what you just said, Alex, because I found as I looked through what is a fairly comprehensive outline that I desperately wanted to flip it back to front because the elephant in the room is really about the global justice issues that are on the table at CIOMS, with the Helsinki rewrite, with Nuffield (?) and Wellcome and other efforts.

And I think that those discussions, which are fundamentally about how to construct ethical trials against background conditions that are fundamentally unjust, of differential access to basic pharmaceuticals, of overlapping and conflicting priorities having to do with intellectual property rights, and industrial

companies, pharmaceuticals in developing countries, that backdrop is something that is the source of the distress that people are feeling and I would actually love to see that moved forward to the very beginning.

Even if the role of this commission is much narrower, even if our audience is within the executive branch to advise on very specific things that they might do to tinker with the system, I think that tinkering has to be done with some knowledge that it is being -- its subject to the changing winds of these international agreements.

Much of the rule -- you know, much of the rule making we have around things like informed consent is premised on notions about the range of choices people have, their freedom to make choices within that range, their capacity to obtain information, and it is not just a matter of cultural differences about autonomy but a matter of developmental differences in terms of their background economies.

I do not think that a discussion about informed consent and what the rules ought to be and what the documentation ought to be could be sensible unless one saw it in the context of whether or not that is really, in fact, an effective protection against a system that might be considered exploitative by virtue

of these background conditions. I appreciate the fact that that might make the report incredibly fuzzy and so I know it is an organizational challenge.

The second thing, and I will try to be briefer now, that occurred to me in terms of topics that we might or might not want to add on, and I also want to mention I understand that unless we get reauthorized some time in the near future this is all highly theoretical.

DR. COX: Based on our most recent report, this is going to be interesting.

MS. CHARO: Yes. Having sat in the audience I would certainly agree with that observation.

MR. CAPRON: Cash your checks as soon as you get them.

(Laughter.)

MS. CHARO: The following questions and possible additions: First, the scope of coverage. Diane's question about the private sector research in the United States which can at times be totally free of federal regulation raises for me the question of whether one might want to focus this report entirely on the pharmaceutical sector because it cleans up certain variables. It will certainly be subject to regulation because it is, in fact, going to be focused on products

that will eventually have to go to the FDA so you are covered by the regs.

Second, it seems to pick up the most emotionally charged issues that have occurred to date. It picks up the ones that have the biggest and most organized financial interests and it picks up the ones that are the subject of the major harmonization efforts. So in some ways it is a wonderful model case but it does mean that when one makes recommendations about our regs, which apply across the board, it would be difficult for us to know at a glance whether or not our recommendations make sense in the nonpharmaceutical context so this is a question. All right.

The second is whether we want to take on the interaction between this and the so-called comprehensive project and discuss the capacity of U.S. local IRB's to handle the tasks that would be assigned to them -- that are assigned to them when it comes to evaluating transnational research.

One of the things that emerged in the Fogarty meeting was that not only are there problems with IRB's in other countries but there are problems with the IRB's here. They are not -- they are not set up for this because they see these protocols rarely.

They do not know the conditions in those countries. They do not have any basis for independent evaluation of the Ministries of Health, the culture, the politics, the local institutions, and once again, as in many other areas, discussion turned around regional IRB's, advising IRB's and national IRB's. There are all these alternatives to the kind of decentralized review we now have, which is terribly burdensome and perhaps not as effective as it could be.

And, finally, on the harmonization and the role of international organizations, I guess I am going to put in a plea similar to the one that I did in the e-mail that went around to members of the commission and that is to please make quite explicit the connections between these rules, the harmonization efforts and trade agreements because this is where the money is. And no matter what we say about ethics I think that follow the money is probably the right advice in understanding what will, in fact, drive changes in the atmosphere as well as in the regulations. And it is not a trivial thing to have a lack of harmony in these regulations. It is a huge issue financially that slows down research.

We have got NAFTA. We have got the EU's own harmonization efforts. We have got the ICH. We have got GATT and we have got the WTO and we have got the

pricing conflicts that I talked about in the e-mail over intellectual property. And I cannot believe that we can really discuss this sensibly while ignoring the economic issues that really are driving the whole field toward harmonization and toward a regulatory system that will be acceptable across countries.

Sorry for going on so long. I had not had a chance to talk for a day-and-a-half. I thought I would do it all now.

(Laughter.)

DR. SHAPIRO: Arturo, David, and Steve? And let me apologize. I have to leave early to catch a plane but Arturo, David and Steve.

Eric will chair in my absence.

DR. BRITO: A couple of comments. I want to make sure that Diane's comment is not lost and what I would like to see in the discussion on chapter four is a little -- some detail about what the legal implications are for nonfederally funded corporations or institutions doing research in Third World countries. What laws do they have to abide to, et cetera, in other countries?

In chapter three when we were discussing the barriers stemming from cultural issues, one of the cultures that I think we often forget about is we tend to say U.S. versus other countries' cultures, and what I

would like to see a discussion of is the scientific versus nonscientific culture. A little more detail on that because I think even within some of the countries, if I remember correctly, with this AZT trial is they were people within the countries that favored more what would be considered U.S. culture, which is really the scientific culture. I mean, I think that is an important issue to discuss there.

And in chapter one in the historical perspective on U.S. sponsored research I would like to see a very positive tone at the beginning of the chapter in terms of discussing the -- what other countries have gained from U.S. sponsored research in those countries because I think if I am not mistaken most of the research done in other countries that is sponsored by the United States has actually benefitted those countries for the most part and it started off with all the abuses or all the problems they have had with the -- that is not the best way to go. So just a positive overtone and maybe giving a historical perspective on some of the positive results from that.

And I had a question for you, Ruth. You mentioned at the very beginning that the AZT trials ended or died a natural death. My recollection of that is that the -- that death came about because of the

attention the media paid to -- in large part because of the attention the media brought to that. Is that what you consider a natural death? I am not sure what you mean by that? And I think that -- otherwise I am not sure the trials would not have ended so suddenly.

DR. MACKLIN: Maybe I misspoke or was not clear. I said the controversy died a natural death. I mean, the trials themselves were halted and because of the benefit it was halted -- the trial in Thailand was halted because the shorter cheaper regimen demonstrated efficacy considerably better than placebo. And then it all died down and everybody went away and both sides claimed victory.

DR. BRITO: In Thailand?

DR. MACKLIN: I mean, both sides in the controversy, yes.

DR. BRITO: My understanding that the trials would have gone on in African countries had not been for the attention drawn on it by the media and I think that is important in there to stress the importance of the media there on a positive light, I guess, that they did bring a lot of attention to it and that is why, I think, those trials ended. Not because the scientific community said it is time to end these trials. Am I accurate in that --

DR. MACKLIN: We need to look at the facts becasue it is my understanding that similar trials are going to be initiated in other countries, in different countries, and that the people defending those trials are claiming we have a different population, we have different nutrition, we have anemia among this population, we do not know whether or not the shorter regimen will work here, et cetera. So that there may be more such trials and I am not certain that looking at the media -- I mean, we have to get the facts and see what happens.

DR. BRITO: Okay. And then the last point I want to make is that when we are discussing the cultural differences, some of the difficulty I have had is that there are some "cultural" differences -- I will put "cultural" in quotes here -- that deny basic human rights to certain people and I am not sure how we can address those within the context of research. So those are my major points.

DR. COX: I have two points. One surrounding comments made by others and then a suggestion.

The first point in terms of comments made by others. I, like Steve and like Alta, really would like to see an emphasis placed on following the money in

terms of the biggest economic impact of these rules and that is in the context not necessarily of the pharmaceutical industry per se but where most of the money is in terms of trade and it does not have to be just in the pharmaceutical industry.

On the other hand, though, I would make the following point: I think that actions of individuals that do not have anything to do with the money can really muddy up the works and could lead to policies and policy changes where the money is that the individual researchers do not have any idea about .

So by putting the focus on where the biggest action is and then looking and saying that -- what are the actions of maybe the smaller players that are really impacting that in a big way, then that turns out to be extremely interesting because it says that the individual is quite important in terms of impacting big changes in ways that they might not recognize.

The final point --

DR. MACKLIN: An example? Could you --

DR. COX: Yes, I am about to do that.

DR. MACKLIN: Okay.

DR. COX: Because the final point, I really completely concur with Alex that specific examples around which this can be woven will definitely have

people understand what the hell we are trying to talk about. So fitting all of that together, here is my recommendation for a specific example:

It is stored tissue samples between the U.S. and China. This is an extremely interesting story that I encourage you to delve into not only from the point of view of the pharmaceutical industry but also from the point of view of individuals. Individuals who are Chinese Nationals who dramatically changed tissue sample policy in China by their personal and private interactions both with the pharmaceutical industry and with academic institutions in the United States.

So I think that there is other examples. That is a specific one I would like to give you because I think it could be woven in, in terms of specifics, to these principles of paying attention to where the money is going, paying attention to actions of individuals, where they think they are only dealing with their own individual research grants but where it changes national policy. This specific example deals with all three of those.

DR. MESLIN: Just as a point of information, it is not reflected in this draft extensively but Elisa Eismann, who you all know is on our staff, is also involved in this project and is going to be gathering

empirical data about the volume and source of funding, both from public sources and to the extent that we are able to do that from private sources. So that will be reflected in some ways not yet in this final outline, which is --

DR. COX: I mean, in summary, and I -- because I do not know, I often times do not make myself clear that the specific examples and how -- not just them as examples but how they impact on the bigger picture of these things I think is often missed. People just think it is the big boys that are making all the difference and little things can impact what those decisions are. We want to pay attention to those.

DR. MESLIN: Steve, and then Alta.

DR. HOLTZMAN: I would like to endorse for several reasons we really think seriously about Alta's points so let me talk about the elephant in the room in two ways. There is -- you mentioned what Elisa is going to look into.

There is a very important empirical question here of -- in terms of the amount of funding and the number of subjects exposed to experimental regimes, when does that -- where is the bulk of that? My gut says it is in pharmaceutical sponsored companies, sponsored research. That the government sponsors subpanels in

insignificance. All right. If the primary charge of this commission in this area is its concern for human subjects research and we talk about the extension of the Common Rule generally and we are specifically dealing where the Common Rule is already effectively extended under FDA, we should go to where the real action is. That is a distinct question about the elephant in the room in terms of economic interests intersecting there but it just so happens it does as well and I think that is great.

I also think it is a wonderful opportunity, following on a theme from last night's dinner, to engage that segment of our society, which because we are a free market economy we have to charge with developing drugs. And I think there is ways one could do this with letters from Harold, all right, to the CEO's of all those major pharmaceutical companies who are up and down the turnpike from him in New Jersey to get them involved. We say how do we get the data? Let's say we want to understand what you do and its impact and let's get them engaged.

DR. MESLIN: Alta? We are getting close to our time.

MS. CHARO: Okay. Two quick things. First, I wanted to just clarify one thing when I talked about

the elephant in the room. I mean, Ruth and I and several others were talking about this before the meeting so it is just for the purpose of the record.

I am talking even more than just the money that is involved in pharmaceutical development, that is to me just an aspect of the trade issues. The elephant in the room for me is the discomfort that is felt in the public about things that could be perceived as exploitative or coercive where the exploitation and coercion is not solely a function of the fact that you have got for profit companies.

It is the fact that you have got richer companies, in poorer countries you have got differential access to health care, you have got devil's bargains in which short-term gain from participation in a trial is nonetheless difficult to swallow because there are alternatives that would be available but for the economic differentials. That is the elephant that I think has got to be the backdrop and then the trade issues play into that issue.

Okay.

DR. HOLTZMAN: But also the elephant in the sense of --

MS. CHARO: Right.

DR. HOLTZMAN: -- who is the people.

MS. CHARO: Right.

The second thing is just informational so it is very quick. One of the things I omitted in terms of stuff that we might want to add in here is the European Data Privacy Directives and their influence in this area because it came up with the tissue sample stuff which is why I remembered it when David mentioned his example. I do not know that it is fully understood yet in terms of its impact.

Steve seems to know more about it than I do.

DR. HOLTZMAN: Specifically the pharmaceutical industry has observed that basically clinical trials arguably would come to a halt.

MS. CHARO: I am sorry. I could not hear.

DR. HOLTZMAN: Clinical trials -- it is problematic in terms of clinical trials whether or not it would require you to break blinds to get people access to their confidential information.

MS. CHARO: Okay. The other informational observation is that at the Comprehensive Report Survey of Federal Agencies' session last time, Marge Speers from CDC talked about some very specific examples of CDC collaboration with other agencies and I do not recall if it was NIH, AID or FDA in which there are examples, in fact, of U.S. agencies or departments finding themselves

in conflict with one another because of sequential reviews with conflicting requirements that play into this issue. So you might find some valuable information there.

DR. MESLIN: I take the prerogative unless there are any other questions to bring the meeting to a close on Harold's behalf.

I will let the commissioners know what I had mentioned to them on e-mail that the staff and the consultants are going to be meeting once the commission has adjourned for the day. We are going to be meeting in this room to start going through our work plan and any commissioners who are interested in sticking around and participating in that discussion, the staff would be grateful to have you join but other than that I thank all the commissioners for coming and the public who was able to attend.

The meeting is adjourned.

(Whereupon, the meeting was adjourned at 12:17 p.m.)

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